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THE ETIOLOGY OF PHLYCTENULAR CONJUNCTIVITIS *

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I. CLINICAL OBSERVATIONS

Phlyctenular conjunctivitis is one of the most frequent eye diseases of childhood. Its appearance in typical cases is characteristic. The grayish nodule in or about the cornea, the injection of the surrounding conjunctival vessels, the lacrimation and photophobia present a picture not easily mistaken. The disease is important not only because of the disability which it produces during its active manifestations, but also because the scarring of the cornea which often results in severe or neglected cases produces permanent injury to vision. In spite of numerous investigations into the cause of this conjunctivitis, the etiology has not been definitely determined. Whether the condition is primarily an eye disturbance, or whether it is one of the evidences of constitutional disease, has long been the subject of lively discussion. Moreover, there has been little uniformity of opinion either among those who have contended for its local character or among those who regard it as a manifestation of disease arising outside the eye. Local bacterial infection from without, exposure to wind and dust, errors of refraction, herpes, eczema, pediculosis, diseased tonsils and adenoids, intranasal conditions, gastro-intestinal disturbance, autointoxication, impairment of general health, bad living conditions, scrofula, the exudative diathesis and tuberculosis have at one time or another been put forward as essential or contributing causes of phlyctenular disease.

Among these numerous conflicting views, a few have attracted particular attention. Early writers on the subject observed its frequent occurrence in that peculiar type of constitution known as scrofula. Beer,[1] in 1813, described the condition under the name of conjunctivitis externa scrofulosa. Mackenzie,[2] in 1833, in an excellent clinical

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1. Beer: Diseases of the Eye, 1813, **2**, 614; cited by Knorr, E. A., and Maldeis, H. J., Etiology of Phlyctenular Conjunctivitis, Maryland Med. Jour., 1913, **56**, 90.

2. Mackenzie, William: A Practical Treatise on the Diseases of the Eye. From last London edition, Boston, Carter, Hendee & Co., 1833, p. 316.

description of the disease, took a somewhat broader view of the etiology, summarizing his opinion in these words, "Without any hesitation we regard the scrofulous constitution as the chief predisposing cause of this ophthalmia; but we must not omit to mention that other remote causes evidently operate in its production; namely, improper diet, want of air and exercise, and insufficient clothing." Such were the generally accepted views until in the enthusiasm of early bacteriologic research, several investigators claimed that the condition arose as the result of local bacterial infection from without. Later researches, however, did not sustain these findings, and during recent years ophthalmologists have become increasingly convinced that systemic causes are the chief factors in the production of phlyctenular disease.

For several years these cases coming to the eye dispensary of the Northwestern University Medical School have been referred by Dr. Brown Pusey to the children's department with the somewhat embarrassing suggestion that the permanent cure of the eye condition depended on proper constitutional treatment. The fact that the usual routine examination failed to reveal any constant systemic disturbance toward which treatment could be directed suggested the present investigation. Moreover, a review of the literature brought out the interesting fact that practically all investigations into the cause of this condition, admittedly a pediatric problem, have been undertaken by ophthalmologists. The study was carried out under the direct supervision of Dr. Joseph Brennemann of the pediatric staff, to whom I am indebted not only for the general plan of the investigation, but also for sympathetic cooperation in every phase of the work.

The series includes ninety-two cases of phlyctenular conjunctivitis, the diagnosis in every case being made by Dr. Pusey. The clinical study included an exhaustive history, painstaking physical examination, and various laboratory tests, with special attention to the numerous views which have been brought forward concerning the cause of this condition. Among these views the following were considered sufficiently important to merit separate discussion: (1) impairment of general health from whatever cause; (2) bad living conditions; (3) gastro-intestinal disturbance; (4) the exudative diathesis; (5) tuberculosis.

IMPAIRMENT OF GENERAL HEALTH

There has been a widespread belief among writers on phlyctenular ophthalmia, based apparently on general impressions rather than accurate data, that the disease attacks especially the less sturdy individuals, or those whose resistance has been temporarily lowered by improper living or previous illness. In securing the history of each case the mother or other attendant was asked whether the patient was

robust, moderately healthy, or delicate. Sixty-four were considered robust, 16 fairly strong, 12 delicate. On physical examination, 52 were found to be well developed and nourished, 28 with fair physique, 12 decidedly below par. Of the 52 who were well developed and nourished, 17 were noted as being unusually good physical specimens. Their bodies were plump, their flesh firm, their color good; in fact, they were much more sturdy than the average healthy child of the same age.

A special effort was made to ascertain whether the patient or his parents associated the eye condition with any constitutional disturbance. When asked what caused the eyes to become sore, the great majority had no idea whatever. Several thought the trouble was brought on by a cold, though on narrower questioning it was frequently found that the nasal discharge which was the usual evidence of the presence of a cold began after the eye became involved, and was, in fact, caused by the profuse tearing of the affected eye. A few stated that measles brought on the attack, while injury, foreign body, stye, fright, bad blood and run-down condition were given in isolated cases. It is significant that those who had had repeated attacks were unable to associate them with systemic disturbance of any kind. That the illness was usually regarded as local in character and trivial in nature was shown by the attitude towards our work. It was not always easy to convince the mother that the child's illness was sufficiently serious to justify an exhaustive history, complete physical examination and laboratory tests.

It was our purpose to determine whether some distinct physical type, or peculiarity of constitution, or a certain train of circumstances preceding an attack could be established in connection with the eye condition; whether, indeed, it migh be possible to say in advance that a given child was a candidate for phlyctenular disease. This we were wholly unable to do. Our cases in general health and development and in the history of previous illness seemed to differ in no particular from patients presenting themselves at our clinic for other complaints.

BAD LIVING CONDITIONS

There is scarcely a writer on phlyctenular disease who omits to mention bad living conditions as a contributing cause. To obtain first hand information concerning the patient's home life, I went into the homes of the first 53 patients studied. The location of the flat or house, the number and size of the rooms, the sleeping rooms, ventilation, surroundings as to light, dust, smoke, etc., were carefully noted. On the data obtained I regarded the living conditions good in 23, fair in 12, poor in 18. Living conditions were considered good only when the family occupied a front flat above ground, with fair light, ventilation, cleanliness and sufficient food. I was especially impressed with

the fact that the appearance of the patients as they present themselves at an outpatient clinic furnishes no criterion for judging home conditions. Coming long distances through dust-swept streets, the hair dishevelled, the face tear-stained and dirty, a soiled handkerchief shielding the affected eye from the light, they would seem to show every evidence of a miserable home environment. Yet on visiting the home I was frequently surprised to find the family in comfortable quarters, the house neat and well-kept, with proper attention to the personal hygiene of the patient. Moreover, in addition to the dispensary cases, the series included 1 nurse in training, 1 medical student, 2 stenographers, and 1 child in the private practice of Dr. Brennemann. Our experience would indicate that bad living conditions are a much less important factor in the production of phlyctenular ophthalmia than is generally taught.

GASTRO-INTESTINAL DISTURBANCE

During recent years intestinal autointoxication has been regarded by many writers as the chief factor in the production of the most varied disorders. In 1905 Elschnig[3] attempted to show that certain eye diseases such as iritis, scleritis and iridocyclitis are due to this cause. Colombo,[4] pursuing the same line of thought, endeavored to establish the importance of auto-intoxication in the etiology of phlyctenular conjunctivitis. The method employed to determine the presence and degree of auto-intoxication was the measure of indican in the urine. In his first paper Colombo reported the finding of indican in the urine in 42 of 43 cases. In a later paper he found indican in large amount in 74 of 115 cases, there being only two in which no indican was detected. That the above findings are not peculiar to phlyctenular conjunctivitis numerous later investigations have abundantly shown. Von Hippe,[5] in studying 416 cases of eye disease, of which 61 were phlyctenular conjunctivitis, found increased indican no more frequently in this condition than in other diseases of the eye. Stuelp,[6] in studying the urine in more than 1,000 cases, including not

3. Elschnig: Ueber Augenkrankungen durch Autointoxikation, Klin. Monatsbl. f. Augenh., 1905, **43,** 417.

4. Colombo, G. L.: Ueber die Pathogenese der ekzematösen Keratokonjunktivitis (skrofulösen), Klin. Monatsbl. f. Augenh., 1911, **49,** 164. Die Autodarmintoxikation in der Pathogenese der ekzematösen Keratokonjunktivitis. *Ibid.*, 1912, **50,** 610.

5. Von Hippel, E.: Ueber Indicanurie bei Augenkranken, Arch. f. Ophth., 1912, **81,** 105.

6. Stuelp, O.: Ist die sog. gastrointestinale Autointoxikation (Indicanurie) eine häufige Ursache von Augenkrankheiten? Arch. f. Ophth., 1912, **80,** 548.

only the most varied eye diseases, but also chronic constitutional diseases, found increased urinary indican in practically the same percentage in each group. In the course of extensive metabolism experiments conducted by Long,[7] Herter,[8] Folin[9] and others, in which quantitative estimation of indican on twenty-four-hour specimens was made daily over long periods of time, it was found that there was considerable variation in the amount of urinary indican from day to day; that some individuals had regularly a greater amount of indican than others on a similar diet, and that all showed less indican when the protein in the diet was reduced. For the sake of completeness a quantitative estimation of indican by the Folin method was made in 17 of our cases with the result that 5 showed no indican, 5 a trace, 4 a small amount, 3 a large amount. From the foregoing reports it is seen that indicanuria in varying degree occurs indiscriminately in phlyctenular conjunctivitis, in other eye diseases, in constitutional disease, and in individuals enjoying robust health. Not only is indicanuria an uncertain sign of intestinal auto-intoxication, the term auto-intoxication itself lacks accurate definition. That it has been all too frequently employed to explain conditions otherwise obscure is now generally admitted. In the words of Jaddassohn, "Where a definite etiologic conception is wanting, the word auto-intoxication interposes itself with well-nigh unerring certainty."

In the present state of our knowledge, a careful history concerning gastro-intestinal disturbance would appear to be the more reliable method of estimating its importance in the production of the conjunctivitis. Ten of the patients had poor appetite at the onset of the attack, one had vomiting spells preceding the onset of repeated attacks, one associated each recurrence of the eye trouble with indigestion. Seven suffered from chronic constipation. The remainder gave no history of digestive disturbance of any kind. Considering the series as a whole, they seemed peculiarly free from complaint referable to the gastro-intestinal tract.

EXUDATIVE DIATHESIS

The frequent association of phlyctenular conjunctivitis with scrofula has already been mentioned. Since advances in our knowledge of tuberculosis have demonstrated that the enlarged cervical glands char-

7. Long, J. H.: Investigations on the Effects of Foods Containing Copper Compounds on the General Health and Metabolism of Man, Report 97, U. S. Dept. Agric., June 16, 1913, p. 213.

8. Herter, C. A.: Influence of Saccharin on Digestion, Metabolism, Nutrition and General Health, Report 94, U. S. Dept. Agric., Nov. 15, 1911, p. 13.

9. Folin, O.: Effect of Saccharin on the Health, Nutrition and General Metabolism of Man, Report 94, U. S. Dept. Agric., Nov. 15, 1911, p. 233.

acteristic of scrofula are invariably tuberculous, the term scrofula has been little used, and then usually as a synonym for tuberculous cervical adenitis. Yet this use of the term does not do justice to the original conception of scrofula. It was not the enlarged cervical glands alone, but also the pasty appearance of the patient, the heavy features, the thickened eyelids, nose and lips, the facial eczema, and the tendency to respiratory catarrh which gave to scrofula its distinctive features; and it is precisely these features that cannot be satisfactorily explained by the presence of tuberculosis alone. Of the children who suffer from glandular tuberculosis, only a small per cent. show the skin lesions characteristic of scrofula. To explain these characteristic lesions, Czerny[10] advanced the theory that there is a congenital abnormal tendency to irritative processes in the skin, mucous membranes and lymphatic tissues appearing in certain children. To this condition he gave the name "exudative diathesis," and taught that when children who suffer from this diathesis become infected with the tubercle bacillus they then exhibit the symptoms of scrofula. He summarizes the symptoms as follows:

> The symptoms manifest themselves on the skin, the mucous membranes and the lymphoid organs. Among the symptoms appearing on the skin are seborrhea, crusta lactea, strophulus and intertrigo; among those on the mucous membranes are geographic tongue, the periodically occurring catarrh of the nasopharynx, pseudocrop, asthma and recurring bronchial catarrh, *phlyctenular conjunctivitis*, balanitis, vulvitis and certain forms of intestinal catarrh. On the part of the lymphoid organs, this diathesis manifests itself through hyperplasia of the tonsils unassociated with infections, hyperplasia of the spleen, or now and then of many lymphoid organs, namely, that condition which by many authors is regarded as a separate clinical picture under the designation status lymphaticus.

Heubner[11] also recognized this condition, and laying stress on the glandular involvement, gave to it the name of lymphatism. Under whatever name it be known, the clinical picture in typical cases is familiar to all students of children's diseases. Yet it becomes at once apparent from the number and variety of the symptoms that the existence of the condition in a doubtful case will be a matter of interpretation on the part of the examiner. If a single symptom were adequate for a diagnosis, few children would escape. What number or grouping of symptoms furnishes positive evidence of the presence of the diathesis? Several of our cases were typical illustrations of this condition, and in some of these the presence of clinically tuberculous cervical glands completed the picture of scrofula. A larger number had facial

10. Czerny, A., and Keller, A.: Des Kindes Ernährung Ernährungsstorungen und Ernährungstherapie, Leipsic and Vienna, 1913, **2**, 352.

11. Heubner, O.: Lehrbuch der Kinderheilkunde, Leipsic, 1911, **2**, 33.

eczema. Altogether about one third of our cases showed some eczema, seborrhea, "cradle cap," bronchial catarrh, glandular swellings, or other evidence of the exudative diathesis, or gave a history of such symptoms. Nor was it often possible to secure a history of insufficient gain in weight during the first few months of life, followed by abnormal fatness, symptoms emphasized by Czerny as important features of the condition. Thus it is seen that the phlyctenular conjunctivitis itself was in the majority of instances the only evidence of the presence of the diathesis. That the skin and mucous membranes of certain children are peculiarly susceptible to irritative lesions, there can be no doubt. It might be expected that the tissues of the eye would share this sensitiveness, and that in such cases phlyctenular conjunctivitis would be prone to occur. But the absence of all other evidence of undue tendency towards irritative processes in so large a percentage of cases of the eye disease is a strong argument against such a tendency being alone sufficient to explain the occurrence of the conjunctivitis. Even assuming that phlyctenular conjunctivitis were a manifestation of the exudative diathesis, it would amount only to a restatement of the problem, for the cause of the so-called diathesis is altogether obscure.

TUBERCULOSIS

The frequent occurrence of phlyctenular disease not alone in scrofulous children, but also in those who showed other clinical types of tuberculosis, suggested the possibility of the conjunctivitis resting on a tuberculous basis. The investigation of this question was made the easier because of the introduction of the cutaneous tuberculin test, which gave a ready means of ascertaining more nearly the full incidence of tuberculous infection. The findings of a number of observers who have applied this test are as shown in the table.

The statistics in Table 1 were based chiefly on the von Pirquet method of applying the cutaneous test. The von Pirquet test was used in our cases with the result that the reaction was positive in ninety, negative in two.

A reaction was considered positive if the vaccinated area showed redness 5 mm. in diameter with a negative control. There was, however, seldom any question concerning a positive reaction. Distinct induration and elevation, as well as redness, at the site of the vaccination were almost invariably observed. In only thirteen of the positive reactions was the diameter of the reddened area less than 1 cm. Many were particularly violent, the inflamed areas being 3 to 4 cm. in diameter with superimposed papules or vesicles. A few showed lymphangitis extending several centimeters up the arm, and in a few cases scab formation occurred after the reaction had begun to recede. Thus there

TABLE SHOWING RESULTS OF TUBERCULIN TEST BY DIFFERENT AUTHORS IN PHLYCTENULOSIS

Author	No. of Cases	No. Positive	Pr. Ct. Positive
Ayrenx[12]	143	128	90
Bednarski[13]	100	100	100
Belenky-Raskin[14]	100	92	92
Bruns[15]	102	62	61
Bywater[16]	12	12	100
Davis and Vaugan[17]	40	28	70
Derby[18]	43	38	88
Pyfer[19]	49	41	84
Rosenhauch[20]	50	48	96
Tivnen[21]	50	46	92
Weekers[22]	156*	142	91
Weekers	58†	32	55
Total	903	769	Av. 85

* Children. † Adults.

was found a surprising difference between these patients and others of the same age not alone in the frequent occurrence, but also in the violence of the cutaneous tuberculin reaction.[23]

It has been frequently stated that a positive von Pirquet is of little significance, because the majority of children give this test. Yet it must be remembered that the scale of infection is a gradually ascending

12. Ayrenx: Ophtalmie phlycténulaire et terrain tuberculeux, Ann. d'Ocult., 1910, **143,** 393.

13. Bednarski: Ueber die Keratoconjunctivitis phlyctenulosa bei Kindern, Klin. Monatsbl. f. Augenh., 1911, **49,** 521.

14. Belenky-Raskin: Zur Aetiologie der phlyktänulären Augenentzündung, Zeitschr. f. Augenh., 1913, **29,** 503.

15. Bruns, H. D.: Phlyctenular Ophthalmia and Its Etiology, Jour. Am. Med. Assn., 1912, **59,** 1002.

16. Bywater, H. H.: A Note on Phlyctenular Disease, Ophthalmoscope, 1910, **8,** 414.

17. Davis, A. E., and Vaugan, H.: Phlyctenular (Eczematous) Conjunctivitis and Keratitis with Special Reference to Etiology and the Value of Tuberculin as a Diagnostic Agent: Together with the Report of Forty Cases, Ophth. Rec., 1912, **21,** 476.

18. Derby, G. S.: The Increasing Importance of Tuberculosis as a Cause of Ocular Disease. The Newer Methods of Diagnosis and the Treatment, Arch. Ophth., 1908, **37,** 515.

19. Pyfer, H. F.: Etiology of Phlyctenular Conjunctivitis and Suggested Treatments, Pennsylvania Med. Jour., **16,** 184.

20. Rosenhauch, E.: Ueber das Verhältnis phlyktänularer Augenentzündungen zur Tuberkulose, Arch. f. Ophth., 1910, **76,** 371.

21. Tivnen, R. J.: Tuberculin as a Diagnostic and Therapeutic Agent in the Treatment of Conjunctivitis Eczematosa, Jour. Am. Med. Assn., 1911, **57,** 1886.

22. Weekers, L.: Nouvelle pathogénie des phlyctènes oculaires, Bull. de L'Acad. roy de méd. de Belgique, 1909, **23,** 577.

23. Positive controls should be employed before accepting a negative von Pirquet test. In vaccinating patients with phlyctenular conjunctivitis after the completion of the above series, I was considerably perturbed by three or four consecutive negative reactions. Persons previously giving a positive reaction were then tested with the same tuberculin with negative results. A representative of the company issuing the tuberculin was interviewed and he said that their recent tuberculin had been found to be inactive and was being recalled.

one reaching the high figures so frequently given only in late childhood. The oft-quoted figures of Hamburger and Monti[24] reported among 82 children between the tenth and fourteenth years a positive tuberculin reaction in 94 per cent. Von Pirquet[25] found 81 per cent. of positive reactions among 193 children of the same age. In 250 children under 6 years, Hamburger and Monti found a positive result in 26 per cent. Von Pirquet in 821 children of the same age obtained a positive reaction in 18 per cent. Numerous American writers have called attention to the fact that the incidence of tuberculosis is greater in European cities than in this country. Veeder and Johnston[26] found in 227 children between the ages of 10 and 14 years at the Children's Hospital in St. Louis a positive reaction in 44 per cent. In 735 children under 6 years, the von Pirquet was positive in 24 per cent. Their figures were compiled from all hospital admissions, including clinical tuberculosis. Excluding these cases the percentage of positive reactions under 6 years was only 12.5 per cent. Even though one accept the higher percentages of tuberculous infection found in European clinics, the figures are in striking contrast to those obtaining for phlyctenular patients of the same age. Thirty-four of Belenky-Raskin's patients with phlyctenular conjunctivitis were under 6 years of age, and 85 per cent. of these gave positive reactions. Weekers found 40 positive reactions in 44 children under 5 years. Among our own cases, 40 occurred in the first five years of life, all but one giving a positive tuberculin test.

In spite of the almost constant presence of tuberculous infection in phlyctenular disease, clinical evidence of tuberculosis has been much less frequently found. A history of direct exposure to tuberculosis was obtained in 29 per cent. of our cases. On physical examination, nine patients showed clinically tuberculous cervical glands or scars from operation, seven had papulonecrotic tuberculids, seven had suggestive findings in the lungs, two had Potts' disease. A distinct D'Espine sign was found in six cases, and in a considerably larger number of cases the findings were suggestive. The total number showing definite clinical signs of tuberculosis equaled 26 per cent.

The presence of tuberculosis in the absence of any other ascertainable cause, either local or general, would suggest that the conjunctivitis rests on a tuberculous basis. Additional facts brought out by Weekers[22] and others strengthen this view.

1. The subcutaneous tuberculin test carried out during an attack of phlyctenular conjunctivitis causes an aggravation of the eye symptoms.

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24. Hamburger, F., and Monti, R.: Die Tuberkulosehäufigkeit im Kindesalter, München. med. Wchnschr., 1909, **56**, 449.

25. Von Pirquet, C.: Frequency of Tuberculosis in Childhood, Jour. Am. Med. Assn., 1909, **52**, 675.

26. Veeder, B. S., and Johnston, M. R.: The Frequency of Infection with the Tubercle Bacillus in Childhood, Am. Jour. Dis. Child., 1915, **9**, 478.

Weekers found in 10 patients so treated that the eye lesions became distinctly worse in eight.

2. Phlyctenules have occasionally occurred following the diagnostic or therapeutic use of tuberculin subcutaneously.

3. Numerous cases of phlyctenular conjunctivitis have occurred coincidentally with or following a positive ophthalmo-reaction. Such cases have been observed by Wiens and Gunther, Fehr, Bonnetiere and Kleinberger, Feer, Gaupp, Citron, Schenck and Seiffert, Krokiewicz, Kraemer, Fertl, Eppenstein, Schrumpf, Freund, Stargardt,[27] and Hamman and Wolman.[28]

4. Weekers performed the ophthalmo-reaction test in five patients who had a history of repeated attacks of phlyctenular conjunctivitis with scars of former lesions, but in none of whom had there been an active process within a year. All of the patients gave a positive reaction, and in three the phlyctenules recurred.

5. Weekers[29] and Stargardt[27] have studied histologically phlyctenules which occurred as a complication of the Calmette reaction, and found that they correspond to those which occur spontaneously.

Assuming that tuberculosis is the essential cause of the conjunctivitis, the immediate secondary causes which provoke an attack are still to be considered. Absorption from tonsillar infection, intranasal conditions, disorders of the teeth or gums and local irritation from without have been thought to have some relation to the attacks. A careful examination of the nose, throat, ears and sinuses was made by Dr. Carl F. Bookwalter, assistant attending otologist, with the result that the presence of adenoids, diseased tonsils, or nasal deformities was not noticeably greater than among other children of the same age. A large percentage had decayed teeth, but here again the number was not greater than among other dispensary children. Nothing in the history of the patient preceding an attack, nor evidence of local or general disturbance on physical examination, could be found with sufficient uniformity even to suggest its being of importance in provoking the conjunctivitis. In one patient who had been under observation in the hospital for a number of weeks with tuberculous glands of the neck, an attack of phlyctenular conjunctivitis occurred when she was in excellent condition, receiving an abundance of good food, gaining rapidly in weight and the glands showing decided improvement. The physical examination was otherwise negative. The absence of demonstrable

27. Preceding authors cited by Stutgardt, K.: Ueber die Wirkung der Einträufelung von Tuberkulin in den Bindehautsack, Ztschr. f. Augenh., 1909, **22,** 1.

28. Hamman, L., and Wolman, S.: Tuberculin in Diagnosis and Treatment, New York, D. Appleton & Co., 1912, p. 209.

29. Weekers, L.: Anatomie pathologique des phlyctènes oculaires, Bull. de L'Acad. roy. de méd. de Belgique, 1910, **24,** 455.

accompanying conditions together with the fact that phlyctenules frequently occur in tuberculous individuals following the use of tuberculin in the eye or subcutaneously would suggest that the condition arises from a disturbance of the equilibrium established between the invading organisms and the host.

The two cases in the series giving a negative von Pirquet deserve special consideration. The first, N. M., a healthy woman, 35 years of age, had a small localized efflorescence on the limbus corneae with moderate injection of the circumcorneal vessels. There had been no previous attack of eye trouble. There was an eruption on the face which had been present for years, diagnosed by Dr. W. A. Pusey as typical acne rosacea. It has been pointed out by various writers that eye lesions in acne rosacea occasionally occur, which closely resemble or are clinically indistinguishable from phlyctenular conjunctivitis. Fuchs[30] says:

> The characteristic mark of phlyctenular conjunctivitis lies in the focal character of the affection as well as in its localization upon and immediately about the cornea. Only one other variety of conjunctivitis, the conjunctivitis ex acne, shares this peculiarity with phlyctenular conjunctivitis. This affection bears the greatest resemblance to the simple typical picture of phlyctenular conjunctivitis. It is possible to make the differential diagnosis chiefly from the fact that conjunctivitis ex acne attacks only adults and those who are at the same time affected with acne rosacea.

The second case, M. H., a girl 21 months old, had a large, distinct, whitish, sharply circumscribed, elevated area on the ocular conjunctiva of the left eye about 2 mm. from the limbus. The surrounding injection occurred chiefly in the larger rather than the finer vessels of the conjunctiva. Dr Pusey stated that although clinically he thought it should be called phlyctenular disease, it was quite different in appearance from those usually seen. It is also significant that there was not the slightest photophobia or lacrimation, symptoms which are usually severe in children of this age. When the patient returned two days later only a trace of the lesion remained, together with slight injection of the surrounding vessels.

The findings in these two cases suggest the possibility that the lesions were altogether different in kind from those ordinarily found in phlyctenular conjunctivitis. ***It is an interesting fact that in no case in which there was a typical efflorescence with characteristic focal injection of the surrounding conjunctival vessels, together with lacrimation and photophobia, was there a negative von Pirquet reaction.***

Finally, the tuberculous theory of the etiology of phlyctenular conjunctivitis brings into harmony the other apparently conflicting opinions of its cause. Impairment of the general health, bad living conditions,

30. Fuchs, E.: Textbook of Ophthalmology (Duane), Philadelphia, J. B. Lippincott & Co., 1911, p. 185.

insufficient food, furnish a favorable opportunity for tuberculosis to gain a foothold. Gastro-intestinal disturbance may be a symptom of obscure tuberculous infection. The exudative diathesis gives a soil favorable to the entrance and growth of the tubercle bacillus which may then produce the clinical picture known as scrofula. These various conditions are seen to be significant inasmuch as they predispose to, or go hand in hand with, tuberculous disease. Their consideration as causative factors strengthens rather than weakens the case for tuberculosis as the one underlying cause of the conjunctivitis.

The foregoing discussion has touched only on the more important features of the clinical study. To make clear the character and scope of the work, and to record data which may be of interest, the outline followed in each case, together with a summary of the findings, is given following:

HISTORY

Age:		Parentage:	
Under 2 years	16	Austrian	6
2 to 5 years	24	German	5
6 to 10 years	24	Irish	4
11 to 14 years	7	Bohemian	3
Over 14 years	21	Croatian	2
Sex:		Lithuanian	2
Male	30	Scotch-Irish	2
Female	62	Russian	2
Parentage:		German-Irish	1
American	27	Spanish-Bohemian	1
Colored	15	Assyrian	1
Polish	12	Belgian	1
Italian	6	Unknown	2

I. Present Illness.—

1. Present acute attack.

a. Patient's or parent's opinion as to cause:

Unknown	59	Eczema	2
Cold	11	Diphtheria	1
Measles	8	Indigestion	1
Injury	3	Fright	1
Styes	2	Run-down condition	1

b. Symptoms:

1. Local

a. Smarting	10	*e.* Photophobia	85
b. Burning	11	*f.* Redness	92
c. Aching	5	*g.* Lacrimation	87
d. Itching	28	*h.* Blepharospasm	11

2. General

a. Malaise	10	*d.* Indigestion	1
b. Headache	2	*e.* Diarrhea	1
c. Appetite poor in	2	*f.* Fever	0

3. Previous attacks:

a. Occurred in			
Worse in winter	3	Worse in summer	7
		Worse in spring	1
b. Accompanying conditions in all attacks:		Eczema	2
		Indigestion	1
Colds	5	Run-down condition	1
Blepharitis	2	Nasal obstruction	1

II. Previous History.—

1. General health:
   - *a.* Robust 64
     Medium 16
     Delicate 12
   - *b.* Subject to colds 39
   - c. Appetite:
     Good 81
     Fair 5
     Poor 2
     Variable 4

2. Is patient different from brothers and sisters in physique, activity, mentality or in susceptibility to colds or other catching disease? (No difference in any of these respects noted with sufficient frequency to be of significance.)

3. Tonsils and adenoids
   Removed 11
   Tonsillitis 7
   Mouth breather 6
4. Running ears 8
5. Eczema 24
6. Acute infections:
   - *a.* Measles 62
   - *b.* Whooping cough 39
   - *c.* Scarlet fever 12
   - *d.* Diphtheria 16
   - *e.* Chicken pox 21
   - *f.* Mumps 10
   - *g.* Pneumonia 6

7. Tuberculosis:
   - *a.* Direct exposure 27
   - *b.* Tuberculous glands 12
   - *c.* Chronic cough 0
   - *d.* Dactylitis 0
   - *e.* Tuberculous joint disease. 3

8. Gastro-intestinal tract:
   - *a.* Habitual constipation 7
   - *b.* Indigestion 3
   - *c.* Acute upsets 2

III. Family History.—

1. Father:
   Well 72
   Tuberculous 4
   Dead (3 of tuberculosis) 13
   Unknown 3
2. Mother:
   Well 77
   Tuberculous 3
   Dead (3 of tuberculosis) 11
   Unknown 1
3. Brothers and sisters:
   Similar eye trouble..... 6
   Tuberculosis 10

IV. Hygiene and Environment.—

1. How long in Chicago? How long in present home?
2. If previously in different part of country or in foreign land, was trouble present there?
3. Number in family, including boarders?
4. How much time does patient spend out of doors?
5. If adult, details as to kind of work and sanitary conditions.
6. Food:
   - *a.* Amounts of vegetables, meats, eggs, milk and sweets.
   - *b.* Use of coffee, tea and alcoholics.
   - *c.* Regularity of meals and eating between meals.
   - *d.* Usual daily menu.
7. Inspection of home (53 cases):
   - *a.* House or flat, front or rear.
   - *b.* Number of rooms, size of each.
   - *c.* Surroundings as to dust, smoke, etc.
   - *d.* Rooms dark or light.
   - *e.* Ventilation.
1. How many in sleeping room with patient?
2. Window open in summer? In winter?
3. Method of heating.

From the foregoing data, living conditions considered:

Good	23	Poor	18
Fair	12		

PHYSICAL EXAMINATION

(Made in every case by Dr. Brennemann)

I. General considerations.—

1. Height, weight, pulse, temperature, respiration.
2. General appearance.

Robust	52	Delicate	12
Moderately strong	28		
3. Evidence of scrofula	9	Evidence of exudative diathesis	17
Evidence of lymphatism	6		

II. Regional examination.—

1. Head:		5. Spine:	
a. Eczema	25	*a.* Pott's disease	2
b. Seborrhea	14	6. Genitalia and Gluteal Region:	
c. Cradle cap	9	*a.* Epididymitis, orchitis	0
d. Pediculosis	10	7. Extremities:	
e. Thickened nose and upper lip	9	*a.* Tuberculous hip	1
f. Excoriation about nostrils	31	*b.* Dactylitis	0
g. Mouth breather	2	8. Glandular system:	
h. Geographical tongue	6	*a.* General adenopathy	6
i. Coated tongue	6	9. Skin:	
j. Decayed teeth	44	*a.* Eczema	25
k. Pyorrhea	11	*b.* Tuberculids	7
2. Neck:		10. Special report on eyes:	
a. Glands		*a.* Eye affected	
1. Palpable	59	Left	34
2. Clinically tuberculous	8	Right	29
3. Chest:		Both	29
a. Heart		*b.* Number of lesions	
Valvular disease	2	Single	51
b. Lungs		Multiple	41
1. Suggestive of pulmonary tuberculosis	7	*c.* Location of lesions	
2. D'Espine sign	6	Cornea	41
4. Abdomen:		Limbus	42
a. Enlarged spleen	3	Conjunctiva	5
		Cornea and limbus	2
		Conjunctiva and limbus	2

11. Special report on nose, throat, ears and sinuses (by Dr. Carl F. Bookwalter):

a. Pathologic tonsils	16	*c.* Otitis media	4
b. Adenoids		*d.* Nose	
Small mass	15	1. Rhinitis	10
Moderate mass	13	2. Swollen septum	2
Large mass	5	3. Deflected septum	3

III. Laboratory examination.—

1. Von Pirquet test:		Strongly positive	65
Weakly positive (reddened area between 5 and 10 mm.)	13	Violent reaction	12
		Negative	2

2. Complete blood count (made in first 40 cases):

No characteristic findings. Two showed eosinophilia. Three a mild secondary anemia. All others within normal limits.

3. Urine examination:

a. Quantitative estimation of indican (17 cases).

None	5	Small	4
Trace	5	Large amount	3

B. EXPERIMENTAL OBSERVATIONS

Although the evidence furnished by clinical study seems conclusive enough, the final proof of the nature of phlyctenular conjunctivitis cannot be established in this way. For by this means alone it is impossible to determine whether one is dealing with an etiologic or pathologic entity, or whether the clinical picture represents merely the way in which the tissues of the eye react to various kinds of irritation. The determination of these points rests on bacteriologic, pathologic, and experimental observations.

The localized character of the conjunctivitis at once suggests the possibility of its being produced by a circumscribed infection from without. In the earlier bacteriologic studies of the eye secretions and of the surface of the phlyctenule, several observers found bacteria which they considered to be of more or less importance in producing the condition. Burchard and von Bach,[31] and Smith[32] stated definitely that the lesion was produced by pyogenic cocci, especially staphylococci. Later investigations by von Bach,[31] Müller,[31] Neumann,[31] Axenfeld[31] and others have shown that the above conclusions were unwarranted. While it is true that the number of organisms in the eye may be increased during an attack of phlyctenular conjunctivitis, this by no means proves that their increase is even remotely concerned in its production. The phlyctenule usually ulcerates, and in such cases, organisms found on the surface of the lesion may well be secondary invaders. As pointed out by Axenfeld,[31] it would be necessary to demonstrate in the contents of very early phlyctenules the regular presence of a definite number of a given kind of organism before this organism could be assumed to be the cause of the disease. Yet he found that in early cases organisms were often absent, and when found were too few in number and too varied in their nature to draw definite conclusions from their presence. Moreover, numerous attempts to produce phlyctenules in healthy animals by the introduction of various organisms into the eye have proved uniformly negative. In the present state of our knowledge, bacteria from without cannot be excluded as a possible cause of the conjunctivitis; proof that they are of importance is altogether wanting.

The microscopic anatomy of the phlyctenule was first studied by Iwanoff[32] in 1869. He showed that the lesion was not a vesicle, as was formerly thought, and as the name phlyctenule itself suggests, but that it consisted of a solid collection of cells. Isolated cases were also

31. Cited by Axenfeld, T.: The Bacteriology of the Eye (MacNab), London, Baillière, Tindall & Cox, 1906, p. 253.

32. Iwanoff, A.: Ueber Conjunctivitis und Keratitis phlyctaenularis, Klin. Monatsbl. f. Augenh., 1869, **7**, 462.

studied by Bass, Gruber, Hertel, Wagemann, Wintersteiner, von Michael, Fuchs, and Leber.[33] Their findings showed considerable variation, due probably in part to the unfavorable conditions under which their material was obtained. The disease is not fatal, it does not require enucleation of the eye, and excision of the phlyctenule as a therapeutic measure has not been seriously advocated. On this account the foregoing studies were restricted almost wholly to cases in which the eye was removed because of some complicating condition, or in which the patient came to necropsy from intercurrent disease. More recently Hayashi and Weekers resorted to the somewhat heroic expedient of excising phlyctenules for microscopic examination, and it is chiefly on their researches that our knowledge of the minute anatomy of the lesion depends.

Hayashi[33] studied five corneal and six conjunctival phlyctenules. In those occurring on the cornea he found the lesion to consist of a collection of leukocytes lying just beneath Bowman's membrane. In early cases the Bowman's membrane and overlying epithelium remained intact. Where the process had progressed farther degeneration and necrosis of the epithelium occurred. In still more advanced cases the more resistant Bowman's membrane had also broken down.

In the conjunctival phlyctenules the cell-collection lay just beneath the epithelium, and in addition to leukocytes, a number of lymphocytes were seen in the lesion, also occasional mast cells and eosinophils. Among the leukocytes larger epithelial cell elements with large pale nucleus and one or several nucleoli were seen. Many of the blood vessels in and about the phlyctenule were distended with blood. Special staining demonstrated the presence of elastic fibers. The epithelium was found to participate in the inflammation. It was irregular, being thinned in places, and in other places thickened and extending into the depth. Its cells were degenerated and not sharply outlined from the underlying tissues. In later cases necrosis and loss of substance occurred.

Weekers'[29] admirable paper reports the histologic findings in twenty-five cases of phlyctenular conjunctivitis. His series included not only cases occurring in typically scrofulous children, but also three in adults in whom tuberculosis was clinically demonstrable, two in children in whom there was a typical Morax-Axenfeld conjunctivitis at the time of the occurrence of the efflorescence, three arising as complications of the Calmette ophthalmo-reaction. In all of these cases the histology was found to be essentially the same. He says in part:

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33. Authors named cited by Hayashi, M.: Beitrage zur pathologischen Anatomie der Phlyktäne und phlyktäneähnlicher Prozesse, Klin. Monatsbl. f. Augenh., 1909, **47**, 557.

The infiltration consists of leukocytes and epithelioid cells. At first the leukocytes are nearly all polynuclear, mononuclears being rare. In the latter period the mononuclears attain the majority. One sees also sometimes in great number and among the leukocytes epithelioid cells having a large pale nucleus. It is not rare to find among the cells of infiltration, most often beneath the epithelium, multinuclear cells, but the number of the nuclei is never large. They are not the real giant cells of the Langhans type, with numerous nuclei disposed *en collerette*. On the other hand, one observes occasionally in the lumen of the altered vessels giant cells with a single protoplasmic mass and numerous nuclei. Special staining showed the presence of mast cells and eosinophils. The cells of the conjunctival tissue take part in the cellular infiltration, as is shown by numerous mitoses. Although the lymphatic capillaries are dilated, the blood capillaries show hypertrophy of their endothelial cells. Their nuclei are large. The cells project markedly into the lumen of the capillaries. The endothelial cells proliferate. Mitosis is seen. It is not rare to see the endothelial cells disposed in several layers even occlude the lumen of the vessel. The outer margin of the capillaries is less changed, and around their circumference are masses of leukocytes and epithelioid cells.

From the beginning of the efflorescence the epithelium participates in the inflammation. The boundary between the epithelium and subjacent connective tissue is not distinct. In the stage of infiltration the epithelium is thickened. The epithelial cells proliferate, as is shown by karyokinesis. The number of layers is increased. Between the epithelial cells are seen many polymorphonuclear cells and lymphocytes. On the deep surface the epithelium sends prolongations into the underlying tissues. One sees in places degeneration of the epithelial cells. In phlyctenules sufficiently old, there is seen one or more excoriations of the epithelium laying bare the subjacent nodule of infiltration.

In addition to the cases cited, Weekers examined two phlyctenules in adults in whom there was no suggestion of clinical tuberculosis, but in whom there was a history of recent syphilis. Histologic examination showed that the changes were particularly noticeable in the epithelium. It was markedly and irregularly thickened. The infiltration of the subepithelial conjunctival tissue was very moderate and composed chiefly of round cells. He believes that the histology of the lesion is sufficiently different from the cases previously examined to suggest that they may be due to a different cause, and raises the question whether they may be a manifestation of syphilis. Yet his description in these cases is so brief that the exact nature of the difference of cell structure is not altogether clear. Moreover, one of the patients gave a positive cutaneous tuberculin reaction. He does not say whether the test was made in the other case.

The uniformity of the lesions in a rather large series of cases, especially since the series included phlyctenules arising under a variety of conditions, namely, in scrofulous children, in tuberculous adults, in children suffering from Morax-Axenfeld conjunctivitis, and in cases arising from the ophthalmic tuberculin test, would suggest that they were due to a common cause. The lesions were not typical tubercle. No tubercle bacilli, true giant cells, or caseation, were observed. Yet their close relation to certain types of tuberculid led Weekers to the conclusion that they are a similar manifestation of tuberculosis.

The conclusions reached by clinical and pathologic study have been strengthened by animal experimentation.

Bruns[34] attempted to produce phlyctenules in rabbits by injecting killed tubercle bacilli into the carotid artery. Thirty-three animals were used. In twelve cases the bacilli were combined with grits of wheat, in five cases with graphite, to increase the probability of organisms finding lodgment in the smaller vessels of the eye. In sixteen cases the bacilli alone were injected. By each of these methods, lesions were produced which resembled phlyctenules clinically, there being all told five successful experiments. Yet Bruns himself admitted that microscopic examination showed important differences between the experimental lesions and human phlyctenules. The lesions did not ulcerate, as usually occurs in phlyctenular disease, and they were found to be distributed throughout the deeper tissues of the eye rather than lying immediately beneath the conjunctival epithelium. Moreover, the microscopic changes showed round cells, epithelioid cells, giant cells, and in some cases clumps of tubercle bacilli. In other words the picture was that of true tubercle. The method employed differed so widely from conditions which obtain in human phlyctenular disease that the experiments would seem to offer little aid in the solution of the problem.

Rosenhauch[20] believed that phlyctenular disease occurred in tuberculous individuals when organisms from without produced localized inflammation in the eye. His experiments were directed toward establishing this hypothesis. He found that when he introduced yellow staphylococci into the eyes of healthy rabbits, no phlyctenules occurred. But when the staphylococci were introduced into the eyes of tuberculous animals, phlyctenules occurred almost as a rule. Inasmuch as no organisms of any kind were found in the phlyctenules, he thought that he might be able to use the toxins from the organisms with the same result. For this purpose he injected twenty healthy animals with tuberculin. Into the eyes of ten he introduced killed staphylococci, into the eyes of the other ten he introduced a filtrate from the organisms. In each of the two experiments, phlyctenules occurred seven times. From his experiments he concludes that phlyctenules arise as the result of the combined action of tuberculous toxins, and that of the toxins of external organisms, especially staphylococcus aureus.

I regret very much that the war made it impossible to secure Weekers' paper in which his experimental results were given. A summary of his findings as reported by Rubert is as follows: His experiments were carried out on tuberculous rabbits. Pure old tuberculin was instilled into the conjunctival sac four to eight times daily. After

34. Bruns, O.: Ueber experimentelle Erzeugung phlyktäneartiger Entzündungen durch abgetötete Tuberkelbaciflen, Arch. f. Ophth., 1904, **58**, 439.

one to three days the conjunctiva became inflamed, and in five cases phlyctenules occurred. Histologically, these phlyctenules showed the same structure as those occurring in scrofulous children. Organisms were not found in the tissues. From his experiments he affirms the tuberculotoxic nature of phlyctenules, but speaks against any etiologic significance of staphylococci, as the phlyctenules arose only when tuberculin was employed. He also introduced tuberculin into the eyes of animals previously injected with tuberculin subcutaneously, but did not obtain phlyctenules in this way.

Rubert[35] repeated the experiments of Rosenhauch and Weekers, and also tried other methods of producing the lesions.

He introduced pure old tuberculin into the eyes of tuberculous rabbits and guinea-pigs. In this experiment in which ten rabbits and thirteen guinea-pigs were employed, three rabbits and two guinea-pigs showed lesions which clinically resembled human phlyctenules. All of the rabbits showed a marked conjunctivitis; intense redness of the bulbar and palpebral conjunctiva, swelling of the plica semilunaris, chemosis of the bulbar conjunctiva, and profuse secretion. The guinea-pigs showed much less sensitiveness to tuberculin, five showing no conjunctivitis whatever.

The animals surviving this experiment were then similarly instilled with staphylococcus vaccine. The rabbits showed a marked conjunctivitis, and in one rabbit and two guinea-pigs phlyctenules appeared.

In another experiment healthy animals which had been previously injected with tuberculin subcutaneously received staphylococcus vaccine and tuberculin in the eyes as in the foregoing experiment. One rabbit showed a phlyctenule in each eye when staphylococcus vaccine was being instilled into one eye, and tuberculin into the other.

Experiments on anemic, weakened, and healthy animals did not produce phlyctenules when staphylococcus vaccine and tuberculin were introduced into the eye in the same manner as in the work on tuberculous animals.

Five of the phlyctenules were examined microscopically. Three were found to consist of round cells, while two in addition to the round cells contained also epithelioid cells. No giant cells, caseation or organisms of any kind were seen. Blood vessels could be seen within the nodule; no alteration of the vessel walls was observed. The overlying epithelium was thinned, the cells were flatter than normal, and in the upper layers the cell nuclei often stained poorly. Ulceration occurred in one case.

Because of the somewhat contradictory findings of the above authors, and in order to extend the observations in directions suggested

35. Rubert, J.: Ueber die Aetiologie der phlyktänulären Augenentzündung, Klin. Monatsbl. f. Augenh., 1912, **50**, 273.

by the clinical study, it seemed desirable to carry out a series of animal experiments. The work was done in the laboratory of Dr. A. I. Kendall and to him and his associate, Dr. A. A. Day, I am indebted for many helpful suggestions.

The work was begun with rabbits and guinea-pigs, but it was soon found that the rabbits were more satisfactory because of the larger size and greater sensitiveness of the eye, and all of the later experiments were carried out on rabbits alone. The order of the experiments was influenced by the desire to conserve material.

EXPERIMENTS

Experiment 1.—July 1-3, 1915. *The Effect of Massage on the Eyes of Healthy Animals.* Three rabbits (1, 2, 3) and three guinea-pigs (1, 2, 3) received three minutes' continuous massage three times daily for three days.

Results.—No evidence of inflammation. Rabbits showed slight hyperemia of palpebral conjunctiva and plica semilunaris immediately following massage, which disappeared within a few minutes. The guinea-pigs showed occasionally a very slight hyperemia of the palpebral conjunctiva, less noticeable than in the rabbits.

Experiment 2.—July 7-9, 1915. *The Effect of the Instillation of Tuberculin Into the Eyes of Healthy Animals.* Twelve rabbits (1-12) and eleven guinea-pigs (1-11) each received 1 drop of pure old tuberculin in the right eye three times daily for three days. Instillations made at 9 a. m., 1 p. m. and 4 p. m. Three minutes' continuous massage followed instillations in half of each group of animals.

Results.—No evidence of conjunctivitis in any case. In the guinea-pigs there was occasional slight hyperemia following massage, though no more than was observed in the first experiment where massage alone was employed. In the rabbits no change was observed when the tuberculin was introduced without massage. When massage was employed, there was regularly a transient hyperemia of the palpebral conjunctiva and plica semilunaris, apparently a little greater than when massage alone was employed. Rabbit 1 was extremely emaciated and appeared very ill during the experiment, yet the eye reacted similarly to those of rabbits in good health.

Experiment 3.—July 26-28, 1915. *The Effect of the Instillation of Staphylococcus Vaccine Into the Eyes of Healthy Animals.* Seven guinea-pigs (2, 3, 4, 6, 8, 10, 11) and eleven rabbits (2-12) each received 1 drop of staphylococcus vaccine in left eye three times daily for three days. Normal salt solution used similarly in right eye as control. Massage was employed in half of the animals. The vaccine was obtained from a culture of *Staphylococcus aureus,* the virulence of which for rabbits was established by the fact that a purulent keratitis resulted when organisms were injected into the cornea. Weight of vaccine, 1 billion per cubic centimeter.

Results.—Guinea-pigs: no conjunctivitis. Occasional slight hyperemia of palpebral conjunctiva following massage, no more noticeable in eye into which vaccine was introduced than in control eye. Pig 8 was very weak and emaciated at beginning of experiment, and died after twenty-four hours. Eyes showed no reaction.

Rabbits: no conjunctivitis. When staphylococcus vaccine was used without massage no change was observed. When massage was employed, there was temporary hyperemia of the palpebral conjunctiva and plica semilunaris but no more marked in the eye into which vaccine was instilled than in the control eye into which normal salt solution was introduced.

Experiment 4.—July 29, 1915. ***The Effect of a Second Instillation of Tuberculin Into the Eyes of Healthy Animals.*** Three rabbits (2, 6, 10) and three guinea-pigs (2, 4, 10) each received 1 drop of pure old tuberculin at 9 a. m., 1 p. m. No massage. These animals had received tuberculin in the same eye three times daily for three days (July 7-9).

Results.—No reaction in any case.

Experiment 5.—July 30-Aug. 25, 1915. ***The effect of the instillation of normal horse serum into the eyes of healthy animals following subcutaneous injection of horse serum; the effect of the injection of normal horse serum subcutaneously following the instillation of horse serum into the eyes.***

Six rabbits (7, 8, 9, 10, 11, 12) and two guinea-pigs (10, 11) were injected subcutaneously with 0.5 c.c. of normal horse serum. Five rabbits (2, 3, 4, 5, 6) and three guinea-pigs (2, 3, 4) received 2 drops of normal horse serum in the right eye.

Twenty-four days later (August 23) Rabbits 2, 3, 4 and 5 and Guinea-pig 4, all of which had received horse serum in the right eye, were injected with 0.5 c.c. of horse serum subcutaneously. The animals which had been injected subcutaneously July 30 received instillations as follows: August 23, Rabbit 7 received one instillation of 3 drops of horse serum. August 24, Rabbit 8 received 3 drops of horse serum in the right eye at 9 a. m., at 1 p. m. and at 4 p. m. August 25, Rabbits 9 and 12 and Guinea-pig 10 received 3 drops of horse serum in the right eye at five-minute intervals for an hour. Rabbits 10 and 11 received 2 drops of horse serum in the right eye at five-minute intervals for two hours.

Results.—No reaction in any case.

Experiment 6.—Aug. 30-Sept. 18, 1915. ***The effect of the instillation of tuberculin and of staphylococcus vaccine into the eyes of healthy animals following the injection of tuberculin subcutaneously.***

Nine rabbits (2, 4, 5, 7, 8, 9, 10, 11, 12) and two guinea-pigs (4, 10) received 1 c.c. of 5 per cent. old tuberculin subcutaneously. Twelve healthy rabbits (13-24), not previously used, received 0.2 c.c. of 5 per cent. old tuberculin subcutaneously. Rabbit 11 died September 1. Rabbits 2, 4, 5 and 9 were killed because of "snuffles." None had shown conjunctivitis.

Beginning September 16, seventeen days after the subcutaneous injection of tuberculin, four rabbits (7, 8, 10, 12) and two guinea-pigs (4, 10) received 1 drop of pure old tuberculin in left eye three times daily for three days. Rabbits 7 and 8 and Guinea-pig 4 were given three minutes' continuous massage following each instillation. Beginning September 21 the remainder of the rabbits received tuberculin in the left eye and staphylococcus vaccine in the right eye as follows:

Rabbits 13, 14, 15, three times daily for two days; 13 and 15, three minutes' massage.

Rabbits 22, 23, 24, three instillations daily for one day.

Rabbits 19, 20, 21, hourly instillations one day from 9 a. m. to 5 p. m. Rabbit 20 had three minutes' massage after each instillation.

Rabbits 16 and 17 were instilled every five minutes for two hours.

The staphylococcus vaccine was from a strain of *Staphylococcus aureus hemolyticus,* which produced pyemia when injected into the ear vein of a rabbit. Weight of vaccine, 1 billion per cubic centimeter.

Results.—No conjunctivitis. Slight transient hyperemia in cases in which massage was employed, and in those instilled every five minutes, due apparently in the latter to frequent manipulation. Rabbits 10 and 15 died shortly after completion of the experiment, and though they had been in poor condition for several days, they gave no reaction.

Experiment 7.—Sept. 30-Nov. 12, 1915. ***The effect of the instillation of tuberculin into the eyes of tuberculous animals.***

September 30, twelve rabbits (8, 12, 13, 14, 16, 17, 19, 20, 21, 22, 23, 24) and two guinea-pigs (4, 10) received 0.1 mg. of a culture of bovine tubercle bacilli intraperitoneally. Temperatures and weights were taken every second day. Guinea-pig 10 died October 19. Necropsy showed generalized tuberculosis. Inasmuch as Rabbits 12, 13, 14, 17, and 22 and Guinea-pig 4 had shown elevation of temperature for several days, instillation of tuberculin was begun October 20. One drop of pure old tuberculin was introduced into the right eye four times daily (9 a. m., 12 m., 2 p. m., 4 p. m.) for three days, except Rabbits 17 and 22, which received three instillations daily during the same period. Rabbits 12 and 13 and Guinea-pig 4 received three minutes' massage following each instillation.

Results.—Guinea-pig 4 showed hyperemia of the palpebral conjunctiva with increased secretion twenty-four hours after beginning the instillation. It died the following day. The rabbits, without exception, showed conjunctivitis, beginning twenty-four to thirty-six hours after the first instillation of tuberculin. The reaction was limited chiefly to the palpebral conjunctiva and was not severe in any case. Rabbit 13 showed also injection of the vessels of the bulbar conjunctiva in the region between 11 and 1 o'clock. The reactions reached their height on the third day, and all had disappeared on the fifth day. Reactions were not noticeably influenced by massage.

October 27. Four rabbits (12, 19, 20, 24) received 1 drop of pure old tuberculin in left eye four times daily for three days. Two rabbits (13 and 22) received 1 drop of pure old tuberculin hourly from 9 a. m. to 5 p. m. during one day. No massage.

Results.—Rabbit 12 died twenty-four hours after beginning the experiment. Eye gave no reaction. Rabbits 19 and 20 showed moderate hyperemia of palpebral conjunctiva. Rabbits 13, 22 and 24 gave a much more marked reaction. In addition to involvement of palpebral conjunctiva, there was redness of the plica semilunaris and ocular conjunctiva with profuse, stringy secretion. October 28, a small, sharply defined circular grayish-white spot just internal to the limbus was seen in the left eye of Rabbit 13. Dr. Pusey pronounced it a tubercle of the iris. The animal died November 3, and microscopic examination confirmed the diagnosis. On the morning of October 29, Rabbit 22 was unable to open the left eye because of the thick secretion which held the lids together. Examination showed intense injection of the palpebral conjunctiva, with mild injection of the circumcorneal vessels. In the inner lower quadrant about 1 mm. external to the limbus there was a grayish, circumscribed, elevated area, pinhead in size, with hyperemia of surrounding vessels. The lesion resembled phlyctenule clinically. Eye enucleated.

November 3. Two rabbits (8, 16) received 1 drop of pure old tuberculin in right eye four times daily for three days.

Two rabbits (19, 21) received 1 drop old tuberculin in right eye eight times daily for three days.

Two rabbits (23, 24) received 1 drop of pure old tuberculin in right eye every fifteen minutes for two hours.

Results.—Rabbits 8, 16, and 21 showed slight injection of palpebral conjunctiva and plica semilunaris eight hours after the instillations were begun. On the following day all rabbits showed violent reactions; intense redness of palpebral conjunctiva and plica semilunaris, moderate injection of the ocular conjunctiva, with profuse, thick secretion. Rabbits 16 and 23 showed more marked injection of ocular conjunctiva in region between 11 and 1 o'clock. Reactions were at their height on the second and third days and disappeared completely on fifth or sixth days. In these cases the reaction seemed about equally severe despite the variation in time interval and the number of instillations made.

November 9. Six rabbits (8, 16, 19, 21, 23, 24) received 1 drop of old tuberculin in left eye four times daily for three days. No massage. Rabbits 19 and 24 had had tuberculin in left eye October 27-29.

Results.—Rabbit 19 was very feeble and emaciated, and showed no reaction. All others gave marked reaction, similar to that heretofore described. November 10 there was seen in Rabbit 8 an indistinct, grayish-white, circumscribed area at the limbus at 6 o'clock, with injection of surrounding vessels. There was also a distinct localized, grayish, raised area the size of a large pinhead on the limbus at 8 o'clock, with hyperemia of the neighboring conjunctival vessels. On the following morning the nodule at 6 o'clock was less distinct, the lesion at 8 o'clock was still plainly visible. The lesion was diagnosed as phlyctenule by Dr. Pusey. Eye enucleated.

Rabbit 23, which had given a very violent reaction, showed on the morning of November 12, one circumscribed, grayish area at 6:30 o'clock, one at 7 o'clock, three close together at 8 o'clock, all situated at the sclerocorneal junction. The lesions were pinhead in size. There was a diffuse injection of the conjunctival vessels, but this was much more marked immediately surrounding the lesions. Eye enucleated November 12.

Experiment 8.—Nov. 18-24, 1915. *The effect of the instillation of staphylococcus vaccine into the eyes of tuberculous rabbits.*

Four rabbits (16, 19, 21, 24) received 1 drop of staphylococcus vaccine in right eye four times daily for three days, beginning November 18. Three of the rabbits (16, 21, 24) received similar instillations in left eye beginning November 22. Vaccine from same source as that employed in Experiment 3. Weight, 1 billion per cubic centimeter.

Results.—Rabbit 16 showed moderate redness of palpebral conjunctiva and very slight injection of ocular conjunctiva on the morning of the second day of instillation into left eye. This was very transient, disappearing within a few hours. Others gave no reaction. Rabbit 19 died twenty-four hours after beginning of experiment.

November 29. Rabbit 24 was very feeble at the conclusion of the foregoing experiment. Others appeared in good condition. Thinking, however, that the failure to react to staphylococcus vaccine might be explained by the fact that the tuberculosis was progressing rapidly, it was decided to ascertain whether the eyes remained sensitive to tuberculin. Instillations were made four times daily for three days.

Results.—Rabbit 24 showed a very mild conjunctivitis, which began to recede on the second day. Rabbit 21 gave a moderate reaction. Rabbit 16 gave a violent reaction beginning six hours after the first instillation. There was marked redness and edema of the palpebral conjunctiva, with injection of the plica semilunaris and bulbar conjunctiva. December 1, three small grayish nodules, pinhead in size were seen on the limbus in the region between 5 and 6 o'clock, with increased injection of surrounding conjunctival vessels. On the following day two of the lesions were still seen distinctly. Eye enucleated.

Experiment 9.—Nov. 25-Dec. 30, 1915. *The effect of the instillations of tuberculin into the eyes of tuberculous rabbits not previously subjected to experimentation.*

Inasmuch as the eyes of the rabbits used as heretofore described had been instilled repeatedly both before and after they were made tuberculous, it might be claimed that the lesions produced were the result of the cumulative action of the various irritants. To meet this possible objection, also to secure, if possible, a greater number of phlyctenules for study, twelve additional rabbits (25-36) were injected with 0.1 mg. of a bovine culture of tubercle bacilli, Nov. 25, 1915. A few days later Rabbits 25, 32 and 36 were killed because of "snuffles."

December 20. Nine rabbits (26, 27, 28, 29, 30, 31, 33, 34, 35) received 1 drop of pure old tuberculin in right eye four times daily for three days.

Results.—Rabbit 30 gave no reaction. Rabbit 33 showed very mild reaction beginning on the third day. There was redness of the palpebral conjunctiva, with moderately increased secretion. All others gave severe reactions similar to those described above when similar instillations were made. December 22,

Rabbit 31 showed localized injection of the lower quadrants of the conjunctiva, and in the region of 5 o'clock, 1 mm. from the limbus, a grayish, circumscribed area pinhead in size. December 23, the same area was still visible, and near it were seen two other grayish areas with narrow hyperemic band leading to them from a peripheral direction. December 24, the lesion at 5 o'clock could be seen indistinctly, the other two had disappeared. December 25, only slight localized hyperemia remained. On the following day this had disappeared.

December 21, Rabbit 35 showed, in addition to generalized conjunctivitis, a marked injection of the larger conjunctival vessels of the lower quadrants of the ocular conjunctiva, also slight, diffuse injection in this region. December 22, there was seen a distinct grayish nodule on the limbus at 6 o'clock. It was the size of a large pinhead and encroached on the corneal tissue. The lesion had the typical appearance of phlyctenule. Eye enucleated December 23.

December 29. The conjunctivitis from the foregoing experiment having disappeared, the eyes of the rabbits were examined preparatory to instilling staphylococcus vaccine into the left eye. In the left eye of Rabbit 31 were seen three beautiful phlyctenules. One about 1 by 2 mm. in diameter was situated 2 mm. from the limbus at 12:30 o'clock, the size of a pinhead, one of same size at the limbus at 8 o'clock. All were distinctly elevated, sharply circumscribed, with slight injection of finer conjunctival vessels immediately surrounding them. In addition, the first was surrounded by a mesh of larger vessels, the second had a vessel leading to it from the periphery, also a vessel extending from it to the first nodule. A branching vessel lay external to the third lesion. On the following day there was seen on the palpebral conjunctiva of the lower lid about 2 mm. from the fornix and about 3 mm. medial to the midpoint between the canthi, a sharply circumscribed, grayish nodule, surrounded by a narrow zone of fine vessels, with one larger vessel leading toward the inner canthus. The branches of this vessel encircled the nodule. Eye enucleated December 30.

The appearance of the efflorescences in this case was precisely that of the typical human phlyctenule. There was no generalized conjunctivitis. No instillation of any kind had been made into the affected eye. The animal had had tuberculin in the right eye the previous week, at which time a severe reaction occurred with three small lesions resembling phlyctenules.

Experiment 10.—Jan. 3-5, 1916. *The effect of the instillation of staphylococcus vaccine into the eyes of tuberculous rabbits. The eye into which the vaccine was instilled not previously subjected to irritation of any kind.*

Seven rabbits (26, 27, 28, 29, 30, 33, 34) received one drop of staphylococcus vaccine in left eye four times daily for three days. Vaccine was obtained from *Staphylococcus aureus* which had been passed through rabbit, producing multiple abscesses. Weight of vaccine, 3 billion per cubic centimeter.

Results.—January 4, Rabbit 34 showed very slight localized circumcorneal injection in the outer lower quadrant. On the following day there was seen a fairly distinct, very small circumscribed grayish area about 0.5 mm. from the limbus in the inner lower quadrant. The area was about 0.5 mm. in diameter and did not appear to be raised. A slight degree of surrounding hyperemia, chiefly in linear direction, extended from periphery to the lesion. On the following day the eye appeared perfectly normal. Other rabbits gave no reaction.

Experiment 11.—Jan. 26, 1916. *The effect of the subcutaneous injection of tuberculin on the eyes of tuberculous rabbits.*

Six rabbits (27, 28, 29, 30, 33, 34) used. Temperature taken at 10 a. m. At 3 p. m. they received old tuberculin subcutaneously as follows:

	Mg.		Mg.
Rabbit 27	0.1	Rabbit 30	1.0
Rabbit 28	0.2	Rabbit 33	5.0
Rabbit 29	0.5	Rabbit 34	10.0

Results.—Temperatures were taken at 10 a. m., January 27, and January 28. No distinct rise occurred in any case, the variation being no greater than on days previous to the injection. The animals showed no evidence of discomfort, and no eye disturbance was observed.

Experiment 12.—Feb. 4, 1916. *The effect of a single instillation of pure old tuberculin into the eyes of tuberculous rabbits.*

Two rabbits (33, 34) received 2 drops of pure old tuberculin in left eye.

Results.—Rabbit 33 did not react. February 5, Rabbit 34 showed mild hyperemia of the palpebral conjunctiva. There was very slight injection of the vessels in the inner lower quadrant of ocular conjunctiva. The reaction persisted for about twenty-four hours.

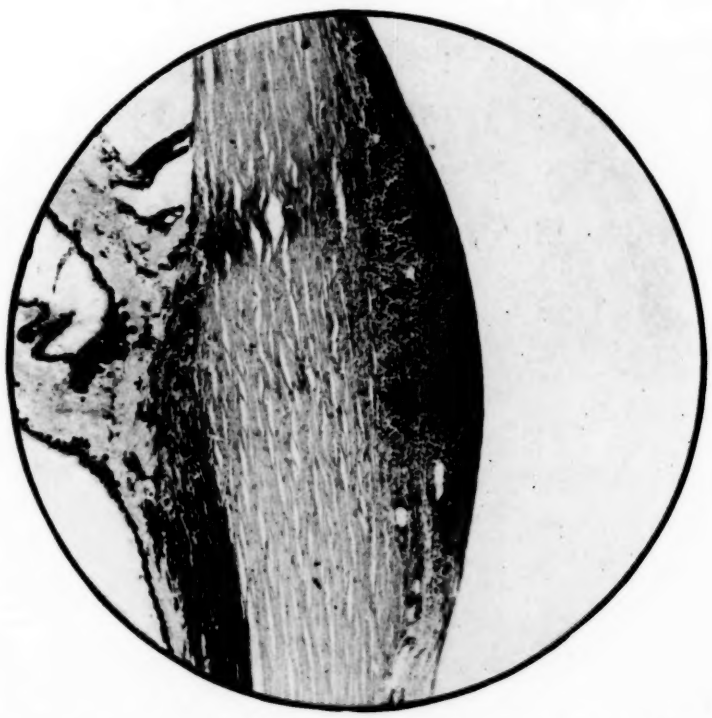

Fig. 1.—Eye 31. Phlyctenule occurring in tuberculous rabbit without instillation of any kind into the affected eye. Photomicrograph × 60.

Experiment 13.—Feb. 4, 1916. *The effect of a single instillation of 1 per cent. old tuberculin into the eyes of tuberculous rabbits (Calmette).*

Three rabbits (27, 28, 29) received 2 drops of 1 per cent. tuberculin in the lefe eye.

Results.—No reaction.

Experiment 14.—March 10, 1916. *The effect of the injection of tuberculin beneath the conjunctival epithelium of tuberculous rabbits.*

Three rabbits (27, 28, 29) used. With a fine needle 1 drop of 10 per cent. old tuberculin was injected beneath the conjunctival epithelium of the right eye. Injection made about 3 mm. from limbus in upper, outer quadrant.

Results.—After twenty-four hours, hyperemia of the conjunctiva occurred around the point of injection. The reactions were not severe, and persisted only about forty-eight hours. There was no generalized conjunctivitis.

Experiment 15.—Feb. 8-April 20, 1916. *The effect of tuberculosis on the eyes of young rabbits.*

The rabbits previously used were sturdy, full-grown animals. Inasmuch as phlyctenular conjunctivitis occurs much more frequently in children than in adults, it was thought that phlyctenules might be produced more readily in growing animals. Twelve half-grown rabbits (37-48) were injected intraperitoneally with 0.05 mg. of a bovine culture of tubercle bacilli on Feb. 8, 1916.

Five of the rabbits (37, 38, 40, 43, 44) were not subjected to further experimentation, but were kept under daily observation until they succumbed to their tuberculous infection.

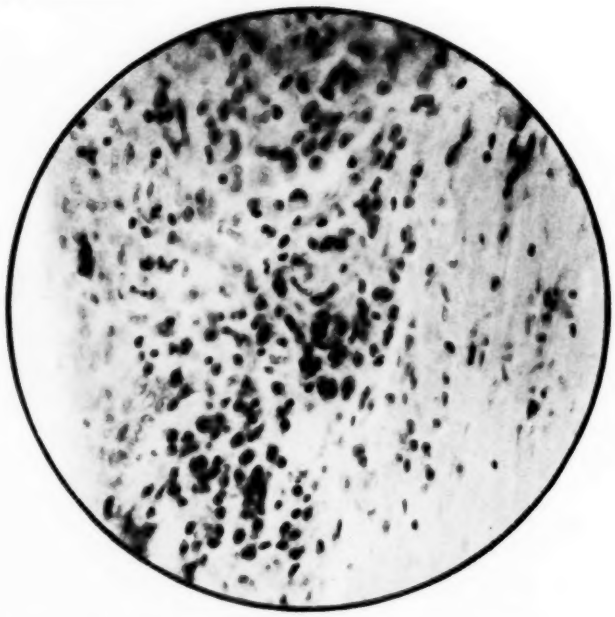

Fig. 2.—Eye 31. High power photomicrograph from section shown in Figure 1. × 350.

Results.—No phlyctenules or other eye disturbances observed.

Experiment 16.—March 9, 1916. *The effect of the subcutaneous injection of very large doses of tuberculin on the eyes of tuberculous young rabbits.*

Four rabbits (45, 46, 47, 48) used. They had shown distinct elevation of temperature for several days. Temperatures taken at 10 a. m. March 9. At 3 p. m. they received pure old tuberculin subcutaneously as follows:

	Mg.		Mg.
Rabbit 45	1	Rabbit 47	100
Rabbit 46	10	Rabbit 48	1 (gm.)

Results.—No eye disturbance observed. Rabbit 46 was in very poor condition at time of injection and died two days later. Other animals showed no evidence of discomfort. Temperatures were taken at 10 a. m. March 10 and 11. No distinct rise occurred, the variations being no greater than on days previous to the injection.

The three surviving animals were not submitted to further experimentation. April 6, there was seen in the left eye of Rabbit 48 a localized hyperemic area adjacent to the limbus at 8 o'clock. At the corneal margin in the midst of the injected region was a grayish circumscribed area the size of a small pinhead, not definitely elevated. On the following day the injection of the conjunctival vessels was less marked, but the nodule was more distinct. Dr. Pusey declared that it was probably a phlyctenule. In addition to the lesion mentioned, there was a small hyperemic area adjacent to the limbus at 2 o'clock. There was no generalized conjunctivitis. Eye enucleated April 7.

April 12, there was seen in the left eye of Rabbit 45 an elevated, circumscribed vesicular lesion, pinhead in size. It was located at the limbus at

Fig. 3.—Eye 48. Phlyctenule occurring in tuberculous rabbit without instillation of any kind into either eye. Photomicrograph ×90.

12 o'clock. The surrounding conjunctival vessels were injected. A diagnosis of herpes conjunctivae was made by Dr. Pusey.

Experiment 17.—April 4, 1916. *The effect of the injection of pure old tuberculin beneath the conjunctival epithelium of tuberculous young rabbits.*

Three rabbits (39, 41, 42) used. With a fine needle 1 drop of pure old tuberculin was injected beneath the conjunctival epithelium of the left eye in the upper outer quadrant.

Results.—Rabbit 39 was in very poor condition and died at the time of injection. After twenty-four hours Rabbits 41 and 42 showed hyperemia of the conjunctival vessels surrounding the point of injection. This hyperemia extended from the corneal margin to the fornix, and in Rabbit 42 there was

also hyperemia of the upper lid conjunctiva. The reaction was at its height on the second day, then gradually disappeared. The rabbits were kept under observation until death without further noticeable eye disturbance.

Necropsy was performed on all animals used in the foregoing experiments. Generalized tuberculosis was found in all cases inoculated with tubercle bacilli, except in a few that died of intercurrent infection before sufficient time had elapsed for tuberculosis to develop. It was not found in any animal which had not been injected with tubercle bacilli.

DISCUSSION

It will be seen from the foregoing experiments that in eight instances lesions occurred which clinically resembled phlyctenules. They were situated at the limbus or in the adjacent conjunctival tissue, and were about pinhead in size. Injection of the surrounding conjunctival vessels was always observed. All occurred in tuberculous rabbits. In six cases the lesions appeared at the height of a more or less severe generalized conjunctival reaction resulting from the instillation of tuberculin. In two cases phlyctenules occurred in the absence of any known local irritation. No instillations had been made into the affected eye, and there was no generalized conjunctivitis. In one (Rabbit 48) the phlyctenule was so indistinct that the clinical diagnosis was made with some reservation. In the other (Rabbit 31) were seen four typical phlyctenules, three on the ocular conjunctiva, and one on the palpebral conjunctiva.

Following the instillation of staphylococcus vaccine into the eyes of tuberculous animals, no reaction was observed save in two instances, when a localized injection of the ocular conjunctiva occurred. The occurrence of the conjunctivitis in only two cases out of many trials, and the fact that similar transient localized inflammations were occasionally observed in control animals, raise the question whether the vaccine produced the reactions. The repeated instillation both of tuberculin and staphylococcus vaccine into the eyes of healthy animals, and animals previously injected with tuberculin, proved altogether negative.

That phlyctenular conjunctivitis may be an anaphylactic reaction has been suggested. Von Szily[36] found that a typical anaphylactic reaction occurred in the cornea when horse serum was injected into the cornea of an animal previously sensitized by subcutaneous injection of horse serum. It seemed desirable to ascertain whether a reaction would occur when the serum was merely instilled into the eye instead of being injected into the cornea, and whether, indeed, phlyctenules might be produced in this way. Results of the experiment were uniformly negative.

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36. Von Szily, A.: Ueber die Bedeutung der Anaphylaxie in der Augenheilkunde, Klin. Monatsbl. f. Augenh., 1913, **51**, 164.

The foregoing findings differ in several particulars from those of Rosenhauch and Rubert. Rosenhauch reported the occurrence of phlyctenules almost as a rule when staphylococci were introduced into the eyes of tuberculous animals, and in the great majority of cases when staphylococcus vaccine was instilled into the eyes of healthy animals previously injected with tuberculin. Yet one reads his paper with a feeling of disappointment. The lesions produced were not described in detail, whether they were accompanied by localized or

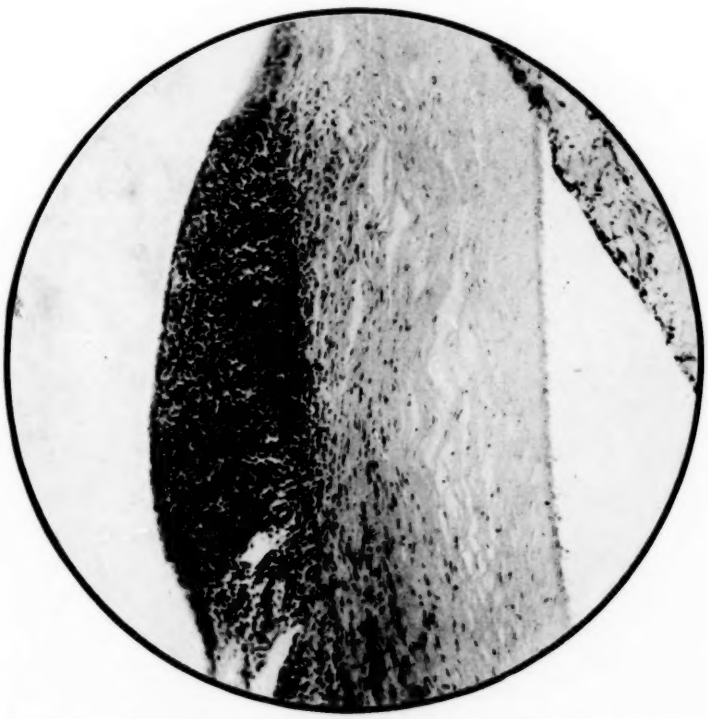

Fig. 4.—Eye 35. Phlyctenule occurring in tuberculous rabbit at the height of a conjunctival reaction resulting from the instillation of tuberculin. Photomicrograph × 110.

generalized conjunctivitis was not stated, and in only two cases were microscopic findings reported. Complete omission of the technic followed made exact repetition of his work impossible. It is regrettable that results so brilliant were so inadequately reported.

Rubert found that instillation of staphylococcus vaccine into the eyes of tuberculous rabbits occasionally produced phlyctenules, and regularly produced a more or less severe diffuse conjunctivitis. Since this did not occur in healthy animals following the instillation of staphylococcus vaccine, he concluded that tuberculosis causes increased

sensitiveness of the eye to various forms of irritation. My experimental studies failed to confirm this conclusion. Save for the specific action of tuberculin, the eyes of tuberculous animals showed no greater sensitiveness than those of healthy animals.

PATHOLOGICAL EXAMINATION

Five eyes showing phlyctenules were studied microscopically. The animals were killed with chloroform, and the eyes enucleated at once. They were fixed in Zenker's fluid, hardened in alcohol, and embedded in paraffin. Sections were stained with hematoxylin and orange G.

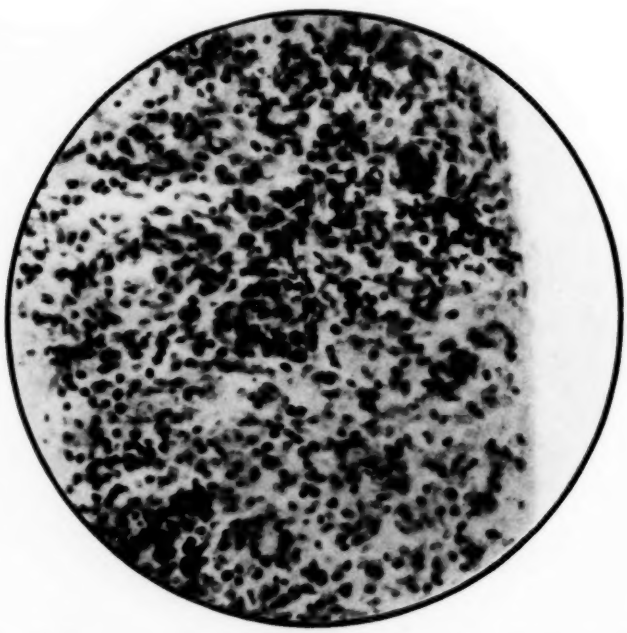

Fig. 5.—High power photomicrograph from section shown in Figure 4. × 350.

Other stains were employed to bring out special features and to examine for organisms. The microscopic anatomy interpreted by Dr. J. P. Simonds is as follows:

EYE 31 (Figs. 1 and 2).—*Phlyctenule occurring in tuberculous rabbit without instillation of any kind into the affected eye.*

Cell Exudate.—The phlyctenule consists of a circumscribed mass of cells lying directly beneath the epithelium, extending peripherally from the corneal margin. The lesion is composed largely of epithelioid cells. These are large, oval or polygonal cells, larger than polymorphonuclear leukocytes, with oval or irregular eccentric nuclei and abundant nongranular cytoplasm. They are identical in all respects with the type of cell described by Mallory as the endothelial leukocyte. Scattered among these cells are a few polymorphonuclear

leukocytes. Near the periphery of the nodule is a zone of round cells of the lymphocyte type. No giant cells or caseation are seen. In the conjunctival tissue outside the phlyctenule are a few plasma cells. (Unna-Pappenheim stain.) In the cell mass are areas in which an occasional cell has undergone necrosis, the nucleus disintegrating by karyorrhexis. A few fibroblasts are seen. Mitoses are fairly frequent.

The blood vessels at the periphery are surrounded by small round cells.

Epithelium.—At the margins of the phlyctenule the epithelium is irregular. Blunt finger-like processes dip into the subjacent tissue. Over the most prominent part of the phlyctenule the epithelium is very thin; the superficial flatter layers are missing. At one point ulceration has occurred. Polymorphonuclear cells are found among the epithelial cells, most numerous near the point of ulceration.

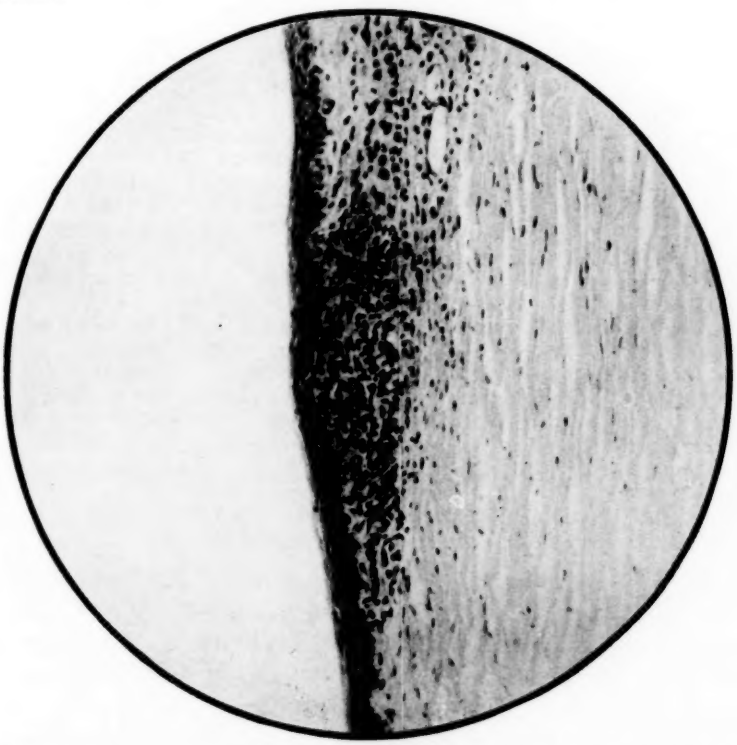

Fig. 6.—Photomicrograph through limbus in Eye 35 at some distance from the phlyctenule. × 180.

The three other phlyctenules occurring in this eye show a structure in all respects similar to that described above, except that in the one on the palpebral conjunctiva there is seen at one point a roughly circular mass of epithelioid cells almost completely surrounded by a zone of small, round, lymphocyte-like cells, thus suggesting in some respects an epithelioid tubercle.

Eye 48 (Fig. 3).—*Phlyctenule occurring in tuberculous rabbit without instillation of any kind into either eye.*

This phlyctenule is smaller than those in Rabbit 31, but its general structure is essentially the same. There are relatively fewer epithelioid cells, anl polymorphonuclear cells are somewhat more abundant. Cell necrosis is seen more

frequently. Occasional mitoses are observed. In places the endothelium of the vessels is swollen, but there is no proliferation. The epithelium is irregular at the margins of the phlyctenule, and thinned over the most prominent part, but it appears intact throughout.

Eye 35 (Figs. 4 and 5).—*Phlyctenule occurring in tuberculous rabbit at the height of a conjunctival reaction resulting from the instillation of tuberculin.*

Cell Exudate.—The phlyctenule is situated at the limbus just beneath the conjunctival epithelium. The lesion consists of a mass of closely packed cells. Epithelioid cells are seen, though much less abundant than in the phlyctenules described. These cells are overshadowed by the larger number of small round cells of the lymphocyte type. Among these are many polymorphonuclear leukocytes. Mitoses are frequent. Plasma cells are present in the neighborhood of the lesion, but not in the cell mass itself.

The endothelium of the capillaries has proliferated. Some of the vessels are partially, others totally occluded by this proliferation, so that the original site of many vessels is indicated by an "endothelial whorl." Polymorphonuclear leukocytes in considerable numbers are seen surrounding the vessels at the periphery of the lesion.

Epithelium.—The epithelium at the margins of the phlyctenule is irregular. Over the summit it is thinner than normal; the superficial flatter layers are missing, but at no point is there a break in continuity. There are present a considerable number of cells filled with mucus, with the nucleus flattened against the base of the cell. Among the epithelial cells are many polymorphonuclear leukocytes.

Eye 16.—*Phlyctenule occurring in tuberculous rabbit at the height of a conjunctival reaction resulting from the instillation of tuberculin.*

Findings are essentially the same as in Eye 35. The changes in the blood vessels are less marked. Epithelioid cells are more abundant toward the periphery, while near the center the small round cells predominate.

Eye 23.—*Phlyctenule occurring in tuberculous rabbit at the height of a conjunctival reaction resulting from the instillation of tuberculin.*

Findings are essentially the same as in Eyes 35 and 16. The chief difference lies in the greater hyperemia and the smaller amount of proliferation of vascular endothelium.

A second phlyctenule which escaped clinical observation is seen in the conjunctiva at some distance from the corneal margin.

The foregoing report shows that in all of the phlyctenules studied the general structure is essentially the same. The lesion is composed chiefly of epithelioid cells and small round cells of the lymphocyte type. Over the summit of the nodule the epithelium is thinner than normal, at the margins it is thickened and irregular. Both in the cell mass and the overlying epithelium polymorphonuclear leukocytes are found. In detailed structure, however, the phlyctenules are sharply divided into two groups. In Eyes 31 and 48, in which the phlyctenules arose in the absence of local irritation from without, the epithelioid cells predominate, with relatively few small round cells. The endothelium of the capillaries shows little change. In the second group, including Eyes 35, 16 and 23, in which the phlyctenules accompanied a severe generalized conjunctival reaction, the epithelioid cells are much less numerous, being overshadowed by the greater number of small round cells. In this group the proliferation of vascular endothelium is a prominent feature.

The microscopic anatomy of these experimental phlyctenules bears a striking resemblance to that described by Weekers[29] and Hayashi[33] in human phlyctenular disease. Neither the human nor experimental phlyctenules show the typical changes of tuberculous tissue as evidenced by the presence of blood vessels and the absence of giant cells, caseation and tubercle bacilli. Yet there is reason to believe that they are tuberculous in origin. Weekers has pointed out the great similarity, both in their mode of occurrence and in their pathology, to certain types of tuberculid. In some of the tuberculids, whose tuberculous origin is extremely probable, no organisms have been found, and some of the features of typical tubercle are lacking. To these tuberculids the phlyctenule bears a close resemblance. Weekers believes that these atypical lesions result from the toxins of the tubercle bacillus rather than from the presence of the organism itself. The frequent occurrence of phlyctenules as a complication of the Calmette reaction, and their production experimentally in animals under similar conditions, lend weight to this view.

In addition to the phlyctenules themselves, an additional interesting condition was observed in Eyes 35, 16 and 23, in which a generalized conjunctival reaction was present. Although the phlyctenules were sharply circumscribed in a peripheral direction, they were not definitely limited in their extent along the limbus, there being a cell exudate of varying intensity throughout its entire circumference. This is shown in Figure 6, which represents a section of Eye 35 at some distance from the phlyctenule. To ascertain whether a similar cell infiltration was present in a conjunctival reaction even in the absence of phlyctenules, a tuberculous rabbit's eye was removed at the height of a conjunctival reaction in which no phlyctenules occurred. A similar cell collection at the limbus was found also in this case.

The character of the exudate differs, however, from that of the phlyctenule itself. The infiltration is composed of small round cells, and of cells about the size of polymorphonuclear leukocytes, having round or slightly oval, deeply staining nuclei and nongranular cytoplasm. The epithelium is not thinned, but in places is thickened and irregular. There are a few polymorphonuclear leukocytes in the cell mass. No necrosis is observed. The endothelium of the capillaries does not show proliferation. Why a cell collection should occur only at the limbus, notwithstanding the fact that the tuberculin comes in contact with the entire conjunctival surface, is not clear. Yet the fact is of special interest, inasmuch as the limbus is the most frequent location of phlyctenular disease.

Thus it is seen that in the phlyctenules occurring at the height of a conjunctival reaction, the clinical picture is that of a more intense

localized reaction superimposed on a generalized conjunctivitis. The pathologic picture is that of a dense localized cell mass superimposed on a cellular exudate of varying intensity which involves the entire circumference of the limbus. The findings do not accurately reproduce those found in human phlyctenular disease, in which sharp localization, both clinically and pathologically, is a distinctive feature. On this account the two instances in which phlyctenules occurred in the absence of local irritation from without are especially significant. For in these two cases the conditions under which human phlyctenules occur seem to have been exactly duplicated. The animals were tuberculous. No instillations had been made into the affected eye. There was no generalized conjunctivitis. The lesions were typical both clinically and microscopically. It is true that in Rabbit 31 tuberculin had been previously instilled into the opposite eye, and Rabbit 48 had received tuberculin subcutaneously. Whether the tuberculin had any influence in producing the phlyctenules it is impossible to say. The fact remains that the tubercle bacillus, or its toxins acting from within, seemed alone responsible for the occurrence of the lesions.

Save for the spcific action of tuberculin, local irritation from without could not be shown to have any part in the production of phlyctenular disease. Organisms in the eye secretions showed no significant changes in number or variety. Of five cultures from the surface of the phlyctenules in Eye 31, taken immediately before enucleation, four were negative; the other showed a single colony of *Staphylococcus albus*. Careful search failed to reveal organisms of any kind within the lesions or on their surface. In early phlyctenules, whether human or experimental, the overlying epithelium is regularly found to be intact. Moreover, in human corneal phlyctenules examined by Hayashi[33] the cell mass was shown to lie beneath Bowman's membrane. In early cases, both Bowman's membrane and the epithelium were unbroken. The absence of even microscopic abrasions of the overlying tissues argues against the invasion of external organisms as a causative factor.

SUMMARY

Clinical observations on ninety-two cases of phlyctenular conjunctivitis revealed the presence of tuberculosis in ninety cases, as shown by a positive von Pirquet test. In the two giving a negative reaction, the diagnosis was doubtful. No other condition, either local or general, could be found with sufficient frequency even to suggest any direct influence in producing the disease.

Phlyctenules were produced experimentally in tuberculous rabbits in eight instances; six times as a complication of a conjunctival reaction resulting from the instillation of tuberculin, twice in the absence of

local irritation of any kind. Numerous attempts to produce the condition in animals not tuberculous were unsuccessful. The pathology of the experimental lesions was similar to that of human phlyctenules. The microscopic findings suggested a tuberculous origin. All clinical, experimental and pathologic evidence points to tuberculosis, and tuberculosis alone, as the cause of phlyctenular disease.

It is with great pleasure that I acknowledge my deep obligation to all who have assisted me in this study: to Dr. Joseph Brennemann for the general plan and personal supervision of the clinical investigations; to Dr. Brown Pusey and his associate, Dr. Robert Blue, for allowing me to use their material, and for much helpful advice; to Dr. Carl F. Bookwalter for examination of the nose, throat, ears, and sinuses; to Dr. A. I. Kendall and Dr. A. A. Day for valuable suggestions in the experimental studies; to Dr. J. P. Simonds for the pathologic examination; and to Mr. M. R. Waltz for preparation of the microscopic sections. The photomicrographs were made by Mr. F. T. Harmon.

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SURGICAL DISEASES OF THE URINARY TRACT IN CHILDREN

WITH SPECIAL REFERENCE TO THE VALUE OF CYSTOSCOPSY *

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It is not generally recognized that children are subject to most of the urologic diseases common to the adult. A review of recent pediatric and surgical literature would lead one to believe that, excluding a few well recognized conditions (as vesical calculus, pyelitis and renal tumors), urinary diseases were very rarely encountered. However, as a result of clinical experiences and postmortem examinations, we are convinced that diagnosis, in affections of the urinary tract, is by no means accurate, and that, in consequence, many cases are overlooked.

The reasons for this are as follows: 1. Diagnosis in general is much more difficult in infancy and childhood. 2. We are deprived of the information obtained by a careful history. Too often we must be guided by fragmentary descriptions of symptoms given by parents or nurses. Unless the condition, therefore, is clear cut with characteristic symptoms (as in vesical stone), it may be impossible to differentiate, by ordinary means, bladder or renal diseases from other affections. 3. Palpation, unless performed under anesthesia, is rather unsatisfactory in children. Then again, palpation is, at times, unreliable as a diagnostic aid, for absence of enlargement of the kidney by no means excludes disease (as in early tuberculosis, and small renal tumors). 4. The modern methods of examination which are considered routine in the adult are seldom applied in the young. The latter probably furnishes the chief reason for the numerous mistakes and uncertainties in diagnosis in this field. Cystoscopy, ureteral catheterization, functional tests, and the roentgen ray have not supplanted the older, time-worn procedures. The subject of urology, in its newer conception, is given scant attention and rarely is reference made to the value of cystoscopy. A number of textbooks ignore these methods, a few describe them perfunctorily, with comments as to impracticality and difficulty. Instead of cystoscopy, it has been suggested that both kidneys be

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* From the surgical service of Mount Sinai Hospital.
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exposed and examined through lumbar incisions before attempting radical operative procedures. This, despite the fact that exploratory exposure of the kidney has often been shown to be of no value. At operation it has frequently been demonstrated that there may be no pathologic changes evident by inspection and palpation, and still serious disease be present (tuberculosis localized in the pelvis or papilla, renal calculus, etc.).

The object of this article is two-fold: first, to call attention to the feasibility of applying in the young in the great majority of cases, the same diagnostic procedures used in the adult, namely, cystoscopy, ureteral catheterization, roentgen ray, cystography, and the functional tests; and second, to the fact that surgical diseases of the urinary tract in infants and young children are not so uncommon as we are led to believe.

CYSTOSCOPY AND URETERAL CATHETERIZATION IN EARLY CHILDHOOD

Nitze[1] was the first to call attention to the use of cystoscopy and ureteral catheterization in children, having, in a few instances, successfully cystoscoped males as young as 8 years of age. In younger children where this examination was urgently indicated and the caliber of the urethra prevented instrumentation, a perineal urethrotomy was advised, through which the instrument could be passed. Casper[2] and Jacoby[3] each described a child's cystoscope, but made no mention of its use clinically. Since then, few articles dealing with this subject have been published. This is probably due to the fact that up to a short time ago, satisfactory cystoscopes of small caliber were not available. At present, when such instruments can be obtained, but few clinics are supplied with the armamentarium necessary for these examinations. In females over 6 years of age, the ordinary adult cystoscope (21 French caliber) may safely be used, for the urethra possesses marked dilatability. In 1908, Portner[4] described a new child's observation and catheterizing cystoscope and reported its successful use in a number of cases. The observation cystoscope has a caliber of No. 12 French, the catheterizing instrument No. 17 French. With these he succeeded in cystoscoping boys of 2, and catheterizing them at 8 years of age. Portner's cystoscopes were found to be unsatisfactory on account of the flexibility of their long shafts. Beer,[5] in 1907, had two instruments made by the Kny-Scheerer firm (Reiniger,

1. Nitze: Lehrbuch der Kystoskopie, 1907, p. 97.
2. Caspar: Handbuch der Cystoscopie, Leipzig, 1911.
3. Jacoby: Lehrbuch der Kystoskopie, Leipsic, 1911.
4. Portner: Deutsch. med. Wchnschr., 1908, No. 43.
5. Beer: Cystoscopy and Ureteral Catheterization in Young Children, Jour. of Surg., March, 1911.

Gebbert and Schall), and published the results of his experiences with them a few years later. The catheterizing cystoscopes are Nos. 15 and 18 French, the observation instruments approximately 10.5 and 12.5 F. caliber. The shafts are made to fit the length of the urethra of a 5-year-old boy (8-10 cm.), and are 9.5 cm. and 12 cm. in length, respectively. Each is so constructed that the catheterizing sheath can be readily detached, making an examining and single catheterizing cystoscope in one. Both have an Albarran finger for guiding the catheter and take a No. 4 to 5 F. The optical system, which is modeled after Nitze, gives a very clear, though small, picture. With these instruments, Beer examined cystoscopically boys of 5 years, and girls as young as 14 months of age. The young child whose ureters were catheterized was a girl 5 years old. These cystoscopes have been in use since 1907 and have been found very serviceable, their great advantage being smallness of caliber and shortness of shaft.

We have records of more than thirty children under 9 years of age who have been cystoscoped during the past few years. The youngest patient was a boy of 17 months who was subsequently operated on for a kidney tumor. The youngest boy catheterized was under 3 years old — the youngest girl 22 months of age.

INDICATIONS AND CONTRAINDICATIONS FOR CYSTOSCOPY IN THE YOUNG

While cystoscopy in young children is devoid of danger, the indications for its application are not as broad as in the adult. The fact that a general anesthetic is required in most cases acts somewhat to restrict its use as a routine diagnostic procedure. It should be reserved for those cases in which surgical affections of the urinary tract are present; or as an aid in differentiating conditions which may be confused with diseases of the urinary organs. Care should be taken to rule out cases with urinary symptoms due to functional disturbances so frequently met with in young children (for example enuresis — hyperacidity of urine). Urinary findings unfortunately cannot be relied on to serve as a reliable guide on which to base indications. At times advanced lesions of the kidney may be present, and the examination of the urine give no intimation of the condition. A pyonephrosis with obstruction of the ureter on the diseased side may show an absolutely normal urine. Cases of congenital stricture of the ureter producing pyonephroses, with negative urinary findings have been reported from time to time in the literature.[6] In tumors of the kidney also the urine frequently fails to contain any abnormal constituents. Pyelitis can generally be

6. Kahn: Congenital Stricture of Ureter Producing Pyonephrosis, Med. Rec., New York, Nov. 16, 1912.

diagnosticated without cystoscopy, and should therefore contraindicate this examination. Every case of pyuria which does not respond to the usual methods of treatment, especially when accompanied by fever, loss of weight and strength, should be cystoscopically examined. Hematuria is also a distinct indication, unless it be proved that the bleeding is but an expression of a hemorrhagic diathesis (purpura hemorrhagica, hemophilia, leukemia, scurvy); or a hemorrhagic nephritis. Renal diseases are often simulated by intraperitoneal conditions; in these cases, cystoscopy is of great value in the differential diagnosis, and its application will often render unnecessary exploratory operations. Before deciding to remove a kidney no matter how badly diseased, the presence of the second should always be ascertained. Cystoscopy is not absolutely essential if the roentgen ray shows the shadow of the other organ. It is of great service when no focal renal symptoms are present, and the kidneys cannot be palpated, in determining the side of the lesion.

Contraindications have been mentioned in discussing pyuria and hematuria. In addition, when the child's condition is such as to preclude a general anesthesia, should this be necessary. Every case, however, must be considered by itself, and if there exists the slightest suspicion that cystoscopy will aid in the diagnosis, it should be used.

Functional test: When ureteral catheterization is not feasible, chromo-ureteroscopy will be found invaluable. It is possible by using this method to make a positive diagnosis in the majority of instances with the ordinary observation cystoscope. Indigocarmin (10 c.c. of 0.4 per cent. solution) is injected about fifteen minutes before the examination, and both meati carefully watched. First the time of appearance of the dye on each side is observed; then the intensity of the color, whether light or dark blue; and lastly, note made of the contractile force with which the colored urine is ejected from the orifice. The latter points are of great importance; a very light blue stream which simply dribbles away is indicative of disease. Normally, the dye appears in ten to fifteen minutes; its absence indicates grave renal impairment. When combined with catheterization, we have the additional data obtained by the examination of the separated urines.

The status of the other functional tests now in vogue has been summed up as follows by Leopold and Bernhard:[7] "Figures for the nonprotein constituents of the blood as well as for the phenolsulphonephthalein excretion of children free from renal disease are practically identical with the figures obtained from adults, and vary within the normal figures as adult figures vary. The changes in these figures in

7. Leopold and Bernhard: The Nonprotein Nitrogenous Constituents of the Blood, and the Phenolsulphonephthalein Test in Children, Am. Jour. Dis. Child., 1916, **11**, 432.

children the subjects of renal disease correspond with the changes observed in adults. The importance of the tests for diagnosis and prognosis amply demonstrated in adults will in all probability, hold true for children." We have not used the phenolsulphonephthalein test in conjunction with cystoscopy and ureteral catheterization, but have confined its use to estimating the total functionating capacity of both kidneys.

TECHNIC OF CYSTOSCOPY AND URETERAL CATHETERIZATION IN CHILDREN

This does not vary much from the routine followed in the adult. Most cases must be examined under narcosis, and a deep anesthesia is generally required before the bladder reflexes are abolished. Occasionally it is possible in very young children, especially girls (3 to 4 years), to use the cystoscope under local anesthesia (novocain). The indigocarmin is injected ten to fifteen minutes before the anesthesia is started. It is often advisable to insert a small catheter into the bladder and wait until the color first appears in the urine before administering the anesthetic. The bladder is then irrigated with a small syringe, and filled with a sterile solution. The capacity of the bladder in a 1-year-old child is approximately 100 c.c., so that 120 c.c. is a safe amount for those over 3 years. As most of the catheterizing instruments for children are single tunneled, but one ureter can be catheterized at a time. It is seldom necessary to catheterize the two. A specimen from the diseased side is generally taken, and the excretion of indigocarmin from the other side noted; this suffices. Occasionally difficulty will be experienced (especially when using a No. 4 catheter) in obtaining a specimen; under such conditions, it is advisable to employ aspiration with a small syringe, or to inject a few cubic centimeters of sterile solution through the catheter, to start the flow.

Roentgenography.—In children, roentgenography is of greater diagnostic value than in the adult and should be used more frequently, especially in cases where the cystoscope cannot be used. Its importance lies in the fact that with good technic the outline of the kidneys can be distinctly shown and deviation in position, size and shape noted. It is at times possible to distinguish an intra-abdominal tumor from renal enlargement.

Cystography.—Roentgenographic studies of the bladder with silver salts, or thorium, is a harmless and often valuable procedure. In chronic vesical retention of urine in children, cystography aids materially in corroborating the diagnosis and in determining the degree of

involvement of the ureters and the kidneys. The bladder is filled with one of the solutions mentioned, the child placed in the Trendelenburg position, and roentgenographed. The roentgenogram shows distinctly in the more advanced cases the considerably enlarged bladder with dilated ureters and renal pelvis. Diverticulae of the bladder are well shown in the cystogram, and a more accurate idea obtained of their size and shape than by cystoscopic examination. The diagnosis of this condition is practically impossible without recourse to one of the two methods mentioned.

In the examination of children suspected of urinary disease, it is advisable, as in the adult, to follow a certain routine. The different steps of the examination should be carried out in their proper sequence, thus avoiding unnecessary repetition. The following has been found the most satisfactory. 1, history; 2, physical examination; 3, urinalysis; 4, roentgenography; if cystoscopy is contraindicated, or cannot be performed — cystography; 5, instrumental examination, which may include bladder catheterization — the stone searcher, and cystoscopy combined with injection of indigocarmin. If cultures of the urine are desired, catheterization is advisable. It is seldom necessary to collect a twenty-four-hour specimen, a single one generally suffices. Roentgenography should include the entire urinary tract, not alone the side towards which suspicion is directed.

The material embodied in this paper is based on a group of thirty-eight cases from the children's surgical wards of Mount Sinai Hospital, and from private records.* The youngest patient operated on was a girl, 11 months of age. This point emphasizes the fact which has been noted in a number of instances, that young children bear major operative procedures on the urinary tract very well. One should not hesitate on account of the extreme youth of the patient to operate, provided the child is in fair condition. As an instance, I may refer to a case recently reported by Kakels,[8] in which an infant, 6 weeks old, had a nephrectomy performed for a large congenital hydronephrosis. Operation was followed by an uninterrupted recovery.

The youngest patient in this group was 11 months old, the oldest, 13 years; the majority of the cases were in children between 4 and 8 years of age.

The series to be described by case reports illustrating the various points previously mentioned, comprises the following surgical diseases of the urinary tract.

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*I wish to thank Dr. Beer for the use of his private records, which have been incorporated in this article.

8. Kakels: Large Congenital Hydronephrosis in an Infant Six Weeks of Age, New York Med. Jour., March 18, 1916.

	Cases
Perinephritic abscess	4
Renal tuberculosis	3
Renal calculus	2
Ureteral calculus	1
Vesical calculus	1
Tumor of kidney (Wilms)	2
Sarcoma of kidney	2
Pyelonephritis (unilateral)	1
Pyelonephritis (bilateral)	2
Hydronephrosis (congenital)	1
Hydronephrosis (traumatic)	1
Suppurative nephritis	1
Subacute nephritis	1
Diverticulum of bladder	1
Chronic vesical retention of urine	12
Nephroptosis	1
Perinephritis (nonsuppurative)	1
Contusion of kidney	1

Perinephritic Abscess.—There were four cases in this series, the youngest an infant of 16 months. Two patients were cystoscopically examined, one a child 20 months of age. The urine was negative in all but one case in which pus and blood were present. The abscess in this instance was caused by the perforation of a cortical abscess of the kidney into the perinephritic tissue. At operation this could be definitely determined. Cultures from the pus in three cases showed *Staphylococcus aureus,* in the fourth *Streptococcus hemolyticus.* The diagnosis is not difficult, and is readily confirmed by aspiration. Cystoscopy is seldem required for corroboration. Incision and drainage effect a cure unless there is marked renal involvement. Two of the patients had crops of furuncles preceding the development of the perinephritic abscess.

REPORT OF CASES

CASE 1.—*Left Perinephritic Abscess.*—P. K., aged 3 years, had measles at 9 months; had furuncles on buttocks a few weeks prior to admission; these disappeared without surgical treatment. After fever, pain in the left loin, and vomiting, physical examination demonstrated a large, tender, fluctuating mass in the left costovertebral angle. On aspiration a thick pus was obtained. Culture showed *Streptococcus hemolyticus.*

Operation consisted of incision and drainage of the perinephritic abscess. The kidney was not explored; tube drainage was instituted. Recovery was uneventful. The patient was discharged from the hospital a few weeks later.

Renal Tuberculosis.—Tuberculosis of the kidney in children is considered a rare disease. Oraison,[9] in 1913, called attention to the fact that but fifty-one cases had been published in the literature. Wildbolz[10] collected 896 cases in which tuberculosis of the kidney, in a surgical form, was clinically recognized forty-eight times. Necropsy findings,

9. Oraison: Jour. d. Urologie.

10. Wildbolz: Chirurgie du Nierentuberculose, Neue Deutsche chirurgie, 1913, **6.**

however, tend to prove that the condition is much more common than clinical statistics indicate. O. Muller[11] found renal tuberculosis thirty-three times in a series of 100 necropsies on tuberculous children, Dickinson,[12] forty-nine times in 300 cases; Rilliet and Barthez[13] found 15 per cent. of 312 tuberculous children had renal involvement. The Berne pathologic institute reports thirteen cases, in a series of 126—almost 10 per cent.

These figures thus indicate that renal tuberculosis in children is not such a rare condition, and that the application of the modern methods of examination would bring more cases to light. In every suspicious case, the urine should be most carefully examined for tubercle bacilli, and if found negative, inoculated into guinea-pigs. In children up to 10 years, the miliary type of tuberculosis predominates; after this age more cases of the chronic cavernous caseating form are observed.

Case 2.—*Right Renal Tuberculosis.*—T. K., a girl, aged 10. The patient had nocturnal enuresis since childhood. For the previous few years she complained of infrequent attacks of pain in the right loin, and for the previous ten months had incontinence and loss of weight.

A poorly nourished child; kidneys not palpable; urine cloudy; albumin + +; considerable pus; cultures negative; tubercle bacilli found in smears; roentgen-ray examination negative.

The cystoscopy and ureteral catheterization showed bladder capacity considerably diminished; around the retracted right ureteral orifice an exudate; left orifice normal; left ureter when catheterized, showed deep indigocarmin concentration in twenty minutes; catheter was left in situ and bladder catheter introduced to obtain a specimen from the right kidney. The urine through this catheter became dark blue in one hour; urine from left kidney contained a few white and red blood corpuscles, hyaline and granular casts; urea 2.4 per cent.; no tubercle bacilli. Bladder urine representing the right kidney revealed white blood corpuscles + + +; few red blood corpuscles; urea, 1.8 per cent.; tubercle bacilli present.

March 3, 1915, nephrectomy for right renal tuberculosis revealed areas of caseating tuberculosis in the upper and lower poles. Incontinence, daily and nocturnal, stopped before the patient left the hospital; convalescence uneventful.

Case 3.—*Left Renal Tuberculosis.*—I. G., 10 years old, had had measles and scarlet fever.

Eight months previous to admission the patient suddenly experienced difficulty in urinating, followed by great frequency and urgency, but no hematuria. The symptoms persisted for three months, then improved somewhat; for the previous three months, he had complained of pain on urination in the end of the penis; passed bloody urine a few times; no lumbar pain.

An anemic child, but otherwise negative. The kidneys were not palpable (under anesthesia). Rectal examination was negative. The urine was cloudy, acid, with many pus cells; albumin +.

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11. O. Muller, quoted by Wildbolz: Chirurgie du Nierentuberculose, p. 4 (Footnote 10).

12. Dickinson, quoted by Wildbolz: Chirurgie Nierentuberculose, p. 4 (Footnote 10).

13. Rilliet and Barthez, quoted by Wildbolz: Chirurgie Nierentuberculose, p. 4 (Footnote 10).

Cystoscopy showed the retrotrigonal area inflamed and in places ulcerated. The left ureter was golf-hole shape; the right ureter was normal, covered with fibropurulent exudate.

Indigocarmin appeared from the right ureter in fifteen minutes, in good concentration. The left ureter was catheterized and purulent urine obtained; there was no indigocarmin secretion. Tubercle bacilli were found in the urine from the left kidney. Roentgen-ray examination showed the left kidney slightly enlarged and ptosed. Nephrectomy was performed later for left renal tuberculosis. An enlarged, adherent, tuberculous kidney was removed; caseating areas were found in the lower pole. Uneventful convalescence.

CASE 4.—*Left Renal Tuberculosis.*—H. H., aged 11 years, was operated on for abscess on the lower end of the spine eight months previous to admission. Four weeks previously the child noticed blood at the end of urination and pain in the end of the penis. Since then he had frequency, urgency and burning.

A fairly well nourished child; kidneys not palpable; marked kyphosis of the lumbar spine; urine acid; slightly cloudy; albumin +; many pus cells and red blood corpuscles; smears negative for tubercle bacilli.

Cystoscopic examination under ether showed the bladder inflamed in the retrotrigonal region; left ureteral orifice did not contract or emit urine; good indigocarmin concentration from the right kidney, which was readily catheterized; no flow from left kidney in thirty minutes; tubercle bacilli found in twenty-four hour specimen; roentgen-ray examination, negative; no enlargement of kidneys. Diagnosis: left renal tuberculosis.

The pathologic report after nephrectomy for left renal tuberculosis showed tubercle bacilli present in the kidneys. Uneventful convalescence.

Urinary Lithiasis.—Not until the advent of radiography was it realized that urinary lithiasis in infants and young children is not an uncommon condition. Before then, it is true, vesical stone was recognized for generations, and its surgical treatment accorded a prominent place in the literature. Renal and ureteral calculi were considered extremely rare, and this is not surprising in view of the fact, that the diagnosis without the Roentgen ray is most difficult. That the condition is frequently overlooked is seen by the statistics of Rafin.[14] He reports a series of 322 cases of renal calculus in infancy; 139 were found at necropsy; 140 occurred in infants under 1 year, twenty-six in children from 1 to 5 years. The small calculi so often present in infancy may be the basis of further trouble in later years.

Vesical calculus is a rather common disease in certain localities. Bokay[15] has collected 1,836 cases of stone in infancy and young children; 1,319 were vesical, one half were urethral, and nine were renal calculi. The diagnosis of vesical calculus offers little difficulty; the rather characteristic syndrome immediately fixes attention to this region. Rectal palpation should always be practiced, and has at times clinched the diagnosis. The stone searcher and cystoscope are valuable aids; the roentgen ray is most important of all. Renal and ureteral stone offer more difficulties; for this reason roentgen-ray examination

14. Rafin: Ann. d. Mal. d. Org. Genito-urinaire, 1911, **29,** 481.
15. Bokay: Ztschr. f. Kinderh., 1912.

should be used in a more routine manner. The presence of sand and gravel in the urine of young children, abdominal pain, spasmodic in character and accompanied by vomiting, are sufficient indications for roentgenography. Roentgen-ray examination should include the whole urinary tract, for stones may be located simultaneously in both kidney and bladder, as in the case to be reported.

CASE 5.—*Renal and Vesical Calculi.*—A. S., a boy. Patient had had measles and paratyphoid fever. Five weeks before admission the child had a sudden attack of retention of urine, and was in another hospital, no diagnosis being made. Nine days before he complained of pain in the right side of the abdomen, very intense at times, but not radiating. There was no frequency or difficulty in urination; he vomited twice. The mother noted that the urine was cloudy.

A well nourished child; abdomen lax and tympanitic; a definite, small, tender mass deep in the right hypochondrium; temperature ranged from 102 to 104; urine amber, cloudy with a trace of albumin and many pus cells; cultures showed *Staphylococcus aureus.* On roentgen-ray examination a triangular shadow was found in the region of the pelvis of the right kidney, and another in the region of the bladder like a calculus. A second examination confirmed this, except that the shadow in the bladder region had moved.

A cystoscopic examination, under ether, showed a calculus on the floor of the bladder. Suprapubic cystotomy was performed. A stone the size of a cherry was removed.

The pelvis of the right kidney was opened and a triangular stone removed. Patient had a stormy convalescence, developing a bilateral otitis media; but was discharged well, with wounds closed.

CASE 6.—A second case of renal calculus was that of a child 6 years of age, whose chief complaint was nocturnal and diurnal enuresis. Roentgen-ray showed distinctly a calculus in the kidney. Cystoscopy was not done; operation was refused.

CASE 7.—*Ureteral Calculus.*—P. E., girl, aged 13 years. March 15, three months previous to admission had cramp-like, intermittent pain in the right lumbar region; no urinary disturbance, no fever, chills or hematuria.

Physical examination revealed a slight tenderness in the lower part of the right iliac region; otherwise negative. The urine was acid, clear, specific gravity 1.028. There were a few white blood corpuscles and a little epithelium. Roentgen-ray examination revealed two calculi present in the right ureter about 1 cm. from the orifice; phenolsulphonephthalein, 45 per cent. in two hours; no red blood corpuscles in centrifuged specimens.

Cystoscopy and ureteral catheterization performed; bladder negative except in the region of the right orifice, which was covered with mucopus; right ureter had an obstruction at 2.5 cm. which was finally passed and bloody urine obtained; no indigocarmin secretion in thirty minutes; in left ureter no obstruction; urine clear; good indigocarmin concentration in twenty minutes. Ureterogram of right ureter demonstrated shadows in the ureter. Extraperitoneal ureterotomy was performed; two stones were removed; convalescence was normal.

Tumors of the Kidney.—The growths most frequently seen in childhood are sarcomas and mixed tumors. The former are probably more common, and are of greater malignancy. The majority occur in early childhood; in a collection of 130 cases, 106 were found in the first five

years, and fifty-seven of these in the first two years of life.[16] Pain is a prominent symptom in sarcoma and is generally severe, whereas in the mixed form, it is only complained of very late in the course of the disease. The tumors rapidly invade neighboring organs; cachexia is rapid. Recurrences or metastases are the rule. The mixed types of tumor (Wilms[17]) are supposed to take origin in embryonic tissue, and are entirely different from other renal growths. They are composed of collections of epithelium in the nature of tubular or glandular structures, and may contain besides smooth and striped muscle fibers, cartilage, fat, bone and proliferating connective tissue. The latter tissue is the one most frequently found. These tumors originate in the substance of the kidney, and grow directly into the parenchyma, but do not infiltrate as the sarcomas or carcinomas generally do. Clinically, they are characterized by their large size (at times filling almost the entire abdominal cavity), absence of pain, and apparent good health of the patient. Often there are no subjective symptoms, and the growth is not discovered until it has reached a very large size. Metastases are rare, although the tumors are exceedingly malignant. The urine usually shows no changes; hematuria when present, is generally microscopic. The disease is most frequently seen in early childhood; occasional cases in the adult are reported. In a series of 165 mixed kidney tumors, 131 appeared within the first 6 years of age. Bilateral cases occur; Walker[18] reports ten instances in 141 cases. The prognosis is bad. Albarran[19] places the mortality from recurrence after operation at 86 per cent., Walker[20] at 93 per cent.

CASE 8.—*Tumor* (Wilms) *of Right Kidney.*—J. M., boy, aged 17 months, fell down a flight of stairs three months previous to admission but sustained no contusions or lacerations; there was no bleeding. About two weeks later the mother noticed a hard mass in the abdomen. This increased in size, but was not painful. Occupying the right half of the abdomen was found a firm, elongated mass, smooth, dull to percussion; the free border extending to the right iliac fossa; seeming to be adherent.

The urine was cloudy, acid, no albumin, few white blood corpuscles and little epithelium. Roentgen-ray shows a homogeneous mass occupying the entire abdomen and part of the false pelvis; it could not be determined roentgenographically what this mass was.

Cystoscopy under ether showed the bladder normal; left ureter discharging concentrated indigocarmin; right ureteral orifice not distinctly seen; no indigocarmin from this side during period of observation; under anesthesia the mass felt nodular, movable and hard.

Nephrectomy for right renal tumor was performed. Normal convalescence; primary union. Pathologic report—Wilms tumor.

16. Holt: Diseases of Infancy and Childhood, 1903.
17. Wilms: Mischgeschwulste, Leipzig, 1899.
18. Walker: Ann. Surg., 1897, **26,** 585.
19. Albarran and Imbert: Les Tumeurs du Rein, Paris, 1903, p. 443.
20. Walker: Ann. Surg., 1897, **26.**

CASE 9.—A second case was that of a child, 3 years old, who had two large hard kidneys. Diagnosis before operation was, either bilateral polycystic kidney or sarcoma. The operation was more in the nature of an exploratory procedure; the sections removed were reported as Wilms tumor.

CASE 10.—*Sarcoma of Kidney.*—F. A., girl, aged 2 years, had pain in the right hypochondrium; no radiation; no difficulty or frequency of urination; mother noticed abdomen becoming larger.

Examination revealed a protuberant abdomen, with visible, hard mass in right upper quadrant, reaching 1 inch below the surface of umbilicus; surface smooth; axillary, cervical and inguinal glands enlarged. The urine was amber, acid, clear, specific gravity 1.016; moderate number of white blood corpuscles; phenolsulphonephthalein, 63 per cent.; urea, 10 mg. per 100 c.c.; urea, 36 mg. per 100 c.c.

Roentgen-ray examination revealed a large, dense, homogeneous shadow which occupied the entire right side of the abdomen, ending near the brim of the true pelvis. The shadow had the outline of an enlarged kidney.

Nephrectomy for sarcoma of right kidney showed the kidney firmly adherent in removing, parenchyma was torn and sarcomatous tissue expressed, radium applied through drainage tract for period of 4,067.5 mg. hours; recurrence and death some months after.

CONGENITAL HYDRONEPHROSIS AND HYDRO-URETER

This is not uncommon in infants and very young children. In a series of 500 cases[21] of hydronephrosis which came to operation, fifty-one were in children 1 to 10 years of age. A large number are found at necropsy — the congenital hydronephrosis of the new-born. The diagnosis may at times be difficult, as is shown by the following cases.

CASE 11.—*Congenital Hydronephrosis.*—W. P., aged 3 years, boy, had malaria one year and measles six months previous to admission. Had had poor appetite for a year, not gaining weight; for the previous ten days complained of hypogastric pains. His mother had noticed that the urine was cloudy.

Heart and lungs were negative; abdomen lax, tympanitic; no dulness, no masses palpable; urine cloudy, acid, specific gravity 1.020, with trace of albumin; many pus cells; negative for tubercle bacilli. Roentgen-ray examination showed the left kidney somewhat enlarged; right kidney normal. Cystoscopy under ether anesthesia showed bladder negative except for congestion in trigone, and slight swelling around the left ureteral region; indigocarmin seen emanating from right ureter in good concentration in fifteen minutes; none from left side in thirty minutes.

At a second cystoscopy one week later these findings were corroborated, and through a lumbar incision a considerably enlarged hydronephrotic kidney and ureter were removed; the ureter was the size of a small gut. Uneventful convalescence.

CASE 12.—Traumatic hydronephrosis occurred in a boy 10 years of age, appearing after the child had been struck by an automobile. A large tumor in the loin was noticed. Cystoscopy demonstrated absence of secretion from the right side; good function from the left. At operation a large hydronephrosis was found; nephrectomy; normal convalescence.

CASE 13.—*Diverticulum of Bladder.*—M. B., boy, aged 10 years, had had diphtheria at the age of 5. Five days before admission he had terminal hematuria, and pain on urinating; had occurred several times since; had some pain in hypogastrium, and felt he could not empty his bladder; slight tender-

21. Küster: Chirurgie der Nieren, Stuttgart, 1902.

ness in right costovertebral angle; right kidney palpable; hypogastrium filled by a globular mass not disappearing completely after urination; distended bladder; penile hypospadias; urine turbid; heavy trace of albumin; much pus and many epithelial cells. Phenolsulphonephthalein test gave color first in thirty-eight minutes; 45 per cent. excretion in two hours; residual urine 100 c.c.; cloudy; tubercle bacilli not found in urine; roentgen-ray examination negative.

Cystoscopy under ether showed the opening of a diverticulum in left bladder wall from margin of which indigocarmin issued; left ureter seemed open within the diverticulum, which was as large as a peach and the mouth of which was thrown into heavy folds.

There was a dilatation of the right ureter.

The diverticulum was found to compress both ureters, accounting for dilatation seen in roentgenogram. It was excised. The left ureter was found markedly distended and intimately adherent to sac, so that about 1 inch of its lower end had to be excised; the proximal end was then implanted into the posterior wall of bladder. Uneventful convalescence; bladder control excellent. Cystoscopy forty-seven days after operation showed the left (implanted) ureter in the median line, and functionating. Indigocarmin appeared in fair concentration in fourteen minutes; on right side in fifteen minutes; site of diverticulum not visible.

SUBACUTE NEPHRITIS

Surgery for this condition should not be undertaken unless all medical means have been tried for some time and found ineffectual. The Edebohls operation is not curative; it is usually undertaken for the relief of general anasarca, or for impending uremia. The patient in our series did not show any improvement after operation and succumbed within a few days. Koplik[22] in 1911 reported a series of five cases in which the Edelbohls operation was performed, with marked improvement in four.

CASE 14. —*Subacute Nephritis.*—A. Z., girl, aged 6 years, was admitted with pronounced edema of eyelids, legs, neck, abdominal wall, and marked ascites; urine, 350 to 400 c.c. daily; many hyaline and granular casts; red and white blood corpuscles. The child did not respond to any form of treatment; edema persisted; urinary output did not increase; patient began to show signs of impending uremia.

On bilateral decapsulation the kidneys were found enlarged and beefy red; the condition gradually became worse, and the patient died two days later.

The diagnosis of this condition is simple and does not require instrumental examination. Despite the fatal termination of this case, numerous favorable reports have been published from time to time, and operation should always be considered, after all methods of treatment have failed.

CASE 15.—*Suppurative Nephritis and Perinephric Abscess, Congenital Stricture of the Meatus and Urethra.*—J. R., boy, aged 7 years, had had scarlet fever four years previous to admission; three years previous to admission had had an attack of difficult urination, with passage of blood and pus; one year later had a similar attack; the urinary stream was always small. Examination revealed tenderness and swelling in left lumbar region; temperature 103 F.;

22. Koplik: Tr. Assn. Am. Phys., 1911.

genital examination disclosed a pin point meatus; urine acid, cloudy, specific gravity 1.014, albumin + +, full of pus and red blood corpuscles. The diagnosis of a perinephric abscess was made, and the patient was immediately operated on. A large abscess containing thick pus was opened, the kidney exposed, and a perforation in the cortex felt near its middle; tube drainage; culture, *Staphylococcus aureus*.

A month later nephrectomy was performed for suppurative nephritis. The kidney was found completely disorganized and studded with multiple suppurative foci. Meatotomy was then performed and instruments up to F. 15 were passed. Uneventful recovery.

CHRONIC RETENTION OF URINE IN CHILDREN

Under this heading are included patients suffering from chronic vesical retention due to various etiologic factors. The condition receives but scant attention in the literature, sporadic cases being reported from time to time. Beer[23] recently published a series of nine cases, and calls attention to the fact that the disease is often unrecognized until a late stage has been reached. The clinical picture is fairly characteristic; the patients have the pale, pasty appearance of chronic nephritis. Difficulty of urination often accompanied by straining, is an early symptom. The bladder is regularly found distended, at times reaching above the umbilicus. Residual urine is present in large amounts. On palpation the bladder can be felt to contract and become hard. The urine is clear in the early stages, but as a rule, becomes infected later on. As a result of back pressure dilatation of the ureters and pelves develop; this can readily be demonstrated by thorium cystograms. Cystoscopy reveals a trabeculation of the bladder with patulous ureteral orifices. Functional tests demonstrate marked renal impairment. Neurologic examination of these patients often shows nothing abnormal, in others distinct evidences of spinal cord or brain lesions are found. In the neuromuscular type instruments pass readily into the bladder without encountering an obstruction. The etiologic factors have been tabulated by Beer as follows:

1. Mechanical obstructions: (*a*) extravesical, as congenital folds and strictures, including tight prepuce, small meatus, new growth. (*b*) Intravesical, as diverticulum of bladder, vesical stone.

2. Neuromuscular: (*a*) brain disease; (*b*) spinal cord disease; (*c*) spasticity of sphincter without definite neurologic signs, probably disease of spinal cord.

The prognosis varies with the type; when due to mechanical factors, surgical procedures are often curative. The neuromuscular group all terminate fatally, generally from renal infection and insufficiency. Operation is only palliative — cystotomy for bladder drainage — and nephrotomy when the kidney becomes infected.

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23. Beer: Chronic Retention of Urine in Children, Jour. Am. Med. Assn., 1915, **65**, 1709.

CASE 16.—*Chronic Retention; Hypertrophied Bladder; Bilateral Hydronephrosis.*—Boy, aged 15 months, with a globular tumor mass in the hypogastrium, always present except when emptied by a catheter; that is, distended, hypertrophied bladder. In the left lumbar region was a mass corresponding to the position of the kidney. This was probably a hydronephrotic organ. No neurologic symptoms were elicited.

Cystoscopic examination revealed bladder trabeculated; otherwise normal; no obstruction in urethra; indigocarmin did not appear until four and three-quarters hours after injection, which suggests a bilateral kidney involvement.

Diagnosis of chronic retention, hypertrophied bladder, bilateral (probably) hydronephroses, due to spasm of vesical sphincter.

PYELONEPHRITIS

It is often difficult, especially in the chronic forms, to differentiate between pyelitis and pyelonephritis. In fact, it has been claimed that there is always involvement of the renal parenchyma in pyelitis. In the acute stage, the clinical manifestations of a pyelonephritis are more pronounced; the fever is higher and remittent in character, and apt to be accompanied by chills; the local signs, tenderness and pain more marked. Pus is present in the urine in varying amounts depending on the location of the abscess. If in the cortex, pyuria may be absent or insignificant. Of considerable diagnostic aid in differentiating these conditions is the late appearance in the urine of blue colored pus after the administration of methylene blue or indigocarmin. Weeks, and often months, after, one or more specimens of urine may suddenly become stained blue, due to the rupture into the pelvis of parenchymatous abscesses which have stored the dye. Beer,[24] who first called attention to this phenomenon, described cases in which methylene blue was excreted as long as two and three-fourths years after its administration.

CASE 17.—*Right Pyelonephritis.*—P. T., a girl, aged 6 years; two months before admission had a bullous eruption on the body; one month later double otitis media and mastoiditis. The patient's urine had been cloudy for two years; complained of urinations every 1 to 2 hours for a few months; for the previous few weeks had had pain in right lumbar region; pain, tenderness and resistance in right flank; temperature fluctuated between 99 and 105 F.; no chills; urine is cloudy; specific gravity 1.020; full of pus; von Pirquet test, roentgen and tubercle bacilli negative.

On cystoscopy the bladder was found diffusely inflamed; the right ureteral orifice swollen, the left normal; both ureters catheterized; no obstruction; right kidney gave fair indigocarmin concentration in twenty-five minutes; catheter became clogged with pus; few cubic centimeters urine obtained; urea 1.1; many white blood corpuscles; left kidney gave good indigocarmin concentration in twenty minutes; urea 0.9; occasional white blood corpuscles.

The child was given large doses of hexamethylenamin. At intervals of two, three and six days, and two weeks following the injection of indigocarmin, after the urine had been clear, the blue color suddenly appeared in one or two

24. Beer: The Diagnosis of Pyelonephritis, Jour. Am. Med. Assn., 1907, **48**, 1936.

specimens. The temperature gradually came to normal, and pus disappeared from the urine. Cystoscopic examination before leaving the hospital, showed very slight cystitis; no pus in catheterized specimen.

The other two cases of pyelonephritis in this series were bilateral, and occurred in female children 22 months and 4 years old, respectively. Both were catheterized, pus obtained from each kidney, and the colon bacillus found in culture in each instance.

CASE 18.—*Retroperitoneal Tumor.*—The following case is cited to illustrate the value of cystoscopy as an aid in differentiating an extravesical from an intravesical condition.

Six days before examination of a boy, 3½ years of age, a large mass was accidentally noted in the hypogastrium, which was hard, solid, nodular, extending from below the umbilicus well down into the pelvis. The question arose whether this tumor was a vesical or prostatic neoplasm or retroperitoneal growth. Cystoscopy demonstrated a normal bladder; both ureteral orifices were normal. Indigocarmin appeared in good concentration from both sides in twelve minutes. The diagnosis of retroperitoneal tumor was made.

CONCLUSIONS

Urologic diseases in children are not as infrequent as we are led to believe. Many of the cases in this series would undoubtedly have been overlooked had not the methods of examinations commonly employed in adults been used. The feasibility of cystoscopy in very young patients, and its practical value are amply illustrated by a study of the case reports. Too much stress should not be placed on negative urinary findings. Cystoscopy will at times be indicated despite the absence of abnormal constituents in the urine.

Of the functional tests, indigocarmin is the simplest in application, and is generally reliable. Its use, combined with the observation cystoscope, will often render catheterization of the ureters unnecessary. Phenolsulphonephthalein and the blood tests (urea-nitrogen) are seldom indicated, unless from a prognostic standpoint. Roentgenography should be more frequently resorted to, and should precede every cystoscopic examination. In obscure vesical conditions, especially when cystoscopy is contraindicated or cannot be performed, cystography will often be found to give valuable information.

The proper application of the methods enumerated will seldom make it necessary to resort to exploratory operations on the urinary tract for diagnostic purposes. Operative procedures on the kidney, ureter or bladder are well borne in infancy and early childhood; in a series of over twenty-five major operations there was but one immediate death, that due to uremia following decapsulation for subacute nephritis.

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SEXUAL PRECOCITY IN THE MALE *

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SYMPTOMS

In sexual precocity of the male we observe as the most striking feature a premature, disproportionate and excessive development of the genitals to the size of those of the full grown man, and also an early development of the secondary sexual characteristics, such as the growth of hairs ad genitalia, ad anum, in the axillae, on the face, and, to a lesser degree, on the remainder of the body, particularly on the extremities; the voice deepens, and in the majority of the cases an increased development of the whole body in length and width with a voluminous musculature (herculean type) and certain psychic features have been noted. This excessive growth, however, is only temporary and the final size of body is not abnormally large, but generally subnormal, since the ossification of the epiphyseal cartilages often occurs prematurely. Thus we observe somatically the ordinary signs of puberty, but at an abnormally early age. In a number of cases this or that symptom was wanting; occasionally there existed obesity.

Whilst in the female at the normal, as well as at the premature age, the time of the gradual onset of the new secretory functions of the sexual glands, that is, the expulsion of a mature ovulum can be determined more or less accurately, due to the accompanying process of menstruation, in the boy the time of the beginning of the secretory function of the sexual glands as manifested in nocturnal pollutions, ejaculations and spermatogenesis, remains as a rule unnoticed. However, the growth of the testes and the penis as a local sign of sexual ripening and the rapid development of the secondary sexual characteristics serve as a more or less reliable symptom of the approaching germinative secretion, the functional capacity.

According to Neurath's[1] publication, only in a few cases of precocity in boys described in the medical literature are to be found exact data as to the onset of emissions and ejaculations of semen.

White,[2] for instance, describes a case of a boy who, at the age of 2 years, practiced masturbation with resulting ejaculation of sperma.

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1. Neurath, R.: Ergebn. d. inn. Med. u. Kinderh., 1909, **4**, 46.
2. White: Med. Chir. Trans., 1815, **1**.

The 13-year-old boy, yet without crines pubis, reported by d'Outrepont, impregnated a girl 9 years old, who still was without the slightest sign of puberty. This latter case demonstrates the well recognized possibility in the female of a very early ripening of impregnable ovula long before the onset of menstruation. Pellizzi[4] in his cases likewise demonstrated the presence of spermatogenesis.

Definite data are also often deficient in the literature about the age in the boy at which the first symptoms of precocity appeared. According to the compilation by Neurath[1] in his monograph, the premature puberty in the male, as far as the respective ages were reported, was completed as follows:

	Cases
At the end of the first year	8
Within the second year	4
Third year	2
Third to fourth year	3
Fifth year	1
Fifth to sixth year	3
Seventh year	2
Eighth year	2
Tenth year	1
Twelfth year	1

In the majority of the more pronounced cases the excessive and rapid growth of the body had begun during intra-uterine life; whilst the premature and rapid development of the genitalia generally took place only some time after birth. On the other hand, sexual prematurity may commence during intra-uterine life, as boys and girls were born with unusually developed sexual parts that afterward continued developing.

In striking contrast to the premature development and excessive growth of the body in precocity is the persistence of the psychic functions in their infantile stage in most cases. Whilst under normal conditions at the period of physical puberty there sets in also a psychic one, a deep psychic alteration and transformation, a period of "storm and stress," often a tendency toward dreaming and reverie, this is not so in cases of prematurity. The children affected may be physically many years in advance of their age; the mind, however, corresponds, as a rule, to the real age; their behavior is childish, but the premature awakening of the vita sexualis lends it a peculiar color. Rarely does the psychic progress take place *pari passu.*

In other instances there exists a delayed mental development, a debility, imbecility or even idiocy, as in the cases of Moreau,[5] Hofacker,[6]

3. d'Outrepont: Quoted from Neurath (Footnote 1).
4. Pellizi: Quoted from Falta (Footnote 31).
5. Moreau: Jour. de méd. de chir. et pharmacol., 1806, **12,** 274.
6. Hofacker: Naturforsch. Versammlung., Düsseldorf, 1903.

Hudoverning,[7] Woods,[8] Ziehn,[9] Morse[10] and the 2-year-old boy mentioned by Heller.[11] Of course, in case of pre-existing weakmindedness, neither in normal nor in premature puberty could any better development of the psychic functions be expected from these biologic processes.

In imbecille and idiotic children the genitalia more often are retarded (Heller) in their development, kryptorchism being here a very common manifestation of degeneracy. In precocious boys often there exist strong sexual impulses, and occasionally masturbation is mentioned. These facts call especial attention to the pelagogic side of the subject.

Excessive sexual impulses in early childhood may, in tainted neuropathics, exist previous to the anatomic development of the generative organs, and independent of physiologic processes; such sexual sensations, premonitions and impulses may then lead to severe masturbation and aggressivity. The occurrence of these isolated, excessive sexual impulses as a result of cerebral (central) processes without adequate peripheral causes represents a type of partial, namely, psychic precocity, included in the term "sexual paradoxia" (v. Krafft-Ebing) since they occur at an age when they should be absent. V. Krafft-Ebing, Fere,[12] Fuchs,[13] Lombroso,[14] Moll,[15] Zambaco[16] and others reported such cases. It is noteworthy that paradoxic sexual impulses have been observed also in animals. Weston[17] reported a six weeks' old colt that used to spring on its own mother when 3 months old; on account of its sexual aggressivity it became so dangerous to other colts and calves that its castration was necessary. The author also mentions masturbation in a colt only 2 months old.

ANATOMY AND ETIOLOGY

Up to the compilation from the literature of Neurath[1] there were seventeen cases of postmortem and four findings during operations in both sexes; fourteen girls and seven boys. Five of these patients presented neoplasms of the sexual organs, ten or eleven demonstrated

7. Hudoverning-Popovits: Gigantisme précoce avec development précoce, Nouv. iconog. de la Salpêtrière, 1903, **16,** 181.
8. Woods, T.: An Extraordinary Case of Early Puberty, Lancet, London, 1882, **2,** 377.
9. Ziehen: Berl. klin. Wchnschr., 1906, p. 1095.
10. Morse: Arch. Pediat., 1913, p. 179.
11. Heller, Th.: Grundriss d. Heilpaedagogik., Leipzig, 1912, p. 172.
12. Féré: Précocité et impuissance sexuelle, Ann. d. mal. d. org. génito-urin., 1906, No. 2, p. 1.
13. Fuchs, Alfred: Jahrb. f. Psychiat. u. Neurol., 1903, p. 207.
14. Lombroso: Arch. di Psichiat. [etc.], Torino, **4,** 22.
15. Moll, Albert: Das Sexualleben des Kindes, Berlin, 1907, p. 107.
16. Zambaco: L'Encephale, 1882, Nos. 1, 2.
17. Weston: Quoted from Moll (Footnote 15), p. 110.

neoplasms of the adrenals, three had tumors of the pineal gland; in one case (Wetzler) there existed hydrocephalus congenitus.

Very interesting is the case in which operation was performed by Sacchi[18] for malign tumor of the testis. At the age of 5 years the boy's left testicle increased to the size of that in the adult, the body grew rapidly, the voice became deep, and hairs grew ad genitalia; at 6 years the development of the body was enormous; at 9 years of age the body length was 143 cm., the weight 44 kilograms; the beard was abundant. The left testis proved, after orchidectomy, to be an alveolar carcinoma. Four months after the operation the beard disappeared, the hairs on the upper lip and genitalia persisted. The voice became again infantile, the penis less large and thick, the sexual impulses, emissions and erections ceased; also the character reverted to the infantile stage.

These tumors of the genitive glands suggest that the irritation of the latter causes an excessive and premature increase of the function of the interstitial tissue of Leydig, hastening the development of the secondary sexual characteristics.

Bulloch and Sequeira[19] compiled ten cases, eight girls and two boys, in which necropsy revealed tumors of the adrenals. One case of precocity in boys was the case of Linser,[20] in which a hypernephroma was found; the testes were of the size of a pigeon's egg and the prostate corresponded in size to that of a boy 15 years old. The other case, observed by Adams,[21] was in a boy not yet 15 years old, who died one year later of metastases of hypernephroma. Later, Glynn[22] brought the number up to seventeen cases in children; fourteen females and only three boys.

According to clinical and pathologic observations, we must ascribe to tumors of the adrenals merely a hastening influence on the development of the secondary sexual characteristics, causing also an excessive growth of the body, since other recognizable functions of the sexual glands, such as menstruation or ejaculation, are not mentioned in these reported cases. It seems that although the hyperfunctionary tumors of the cortex of the adrenals in the young give rise to greatly accelerated growth of the body and to premature development of secondary sexual characteristics, as a rule, it is so without any manifestation of a secretion of the generative cells. In such cases, with Tandler and Gross one might think of a premature function of the *Zwischensubstanz* without premature development of the germinative cells.

18. Sacchi: Riv. sper. di freniat., 1895, **21.**
19. Bulloch and Sequeira: Tr. Path. Soc., London, 1905, **56.**
20. Linser: Beitr. z. Klin. Chir., 1903, **37,** 282.
21. Adams, Ch.: Tr. Path. Soc., London, 1905.
22. Glynn: Quart. Jour. Med., 1912, **5,** 157.

In five cases, all boys, reported by Gutzeit, Cyrill Ogle[23] (sarcoma), Oestreich-Slawyk,[24] Frankl-Hochwart[25] and Raymond Claude,[26] postmortems revealed teratomas of the pineal gland; Horrax's[27] case revealed at postmortem a struma of the pineal. It is not a mere coincidence, probably, that the pineal tumors were found only in *male* precocious children, whilst the adrenal hypernephromas are five times more frequent in the female than in the male.

The relation between genital hypertrophy and the pineal gland, according to Marburg,[28] is perhaps to be interpreted as due to a premature decrease of the functionating glandular tissue, which otherwise under normal conditions undergoes degeneration, beginning with the seventh year of life. The trophic disturbance, that is, the premature development, or as Pelizzi[4] terms it, the macrogenitosomia praecox, may be considered as a manifestation of the insufficiency (*Ausfall*) of the epiphyseal gland. We have to presume that in childhood normally the pineal gland exerts an inhibitory influence on development, and that later the influence gradually diminishes and disappears, due to the partial involution of the gland. This interpretation of the premature development being due to hypopinealism finds its support in the results of experiments by Foa,[29] who, after extirpation of the epiphyseal gland in young roosters, observed a premature and excessive development of the testes and some secondary sexual characteristics.

The reports of positive findings made by Horrax[27] are in keeping with those of Foa.[29] The pinealectomized male guinea-pigs showed a hastened development of the sexual organs, manifested before maturity by a relative increase in size and weight, both of the testes and seminal vesicles, over control pigs of the same litter. The pinealectomized females appear to show a tendency to breed earlier than control animals.

On the other hand, extirpation of the generative glands in young animals has been followed by atrophy of the pineal gland (Biach and Hulles[30]). The case of Marburg[28] also supports the supposition of the epiphyseal gland exerting an influence on the premature sexual development. The examination of the brain of the 9-year-old idiot with well developed crines pubis revealed a markedly inhibited development of the pineal gland, with entirely fetal cell-islands and a marked glia-plaque in its interior.

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23. Ogle, Cyrill: Tr. Path. Soc., London, 1899, **50,** 4.
24. Oestreich-Slawyk: Virchows Arch. f. path. Anat., 1899, **157,** 475.
25. Frankl-Hochwart: Deutsch. Ztschr. f. Nervenh., 1909, **37.**
26. Raymond-Claude: Bull. de l'Acad. d. méd., Paris, 1910, **63,** 265.
27. Horrax: Arch. Int. Med., 1916, **17,** 607, 645.
28. Marburg: Ergebn. d. inn. Med. u. Kinderh., 1909, **4.** Ibid., 1913, **10,** 146.
29. Foa: Arch. Ital. de biol., 1912, **57,** 233.
30. Biach and Hulles: Wien. klin. Wchnschr., 1912, No. 10, p. 373.

Marked hydrocephalus was found post mortem in the 8½-year-old girl reported by Wetzler. As early as in the sixth year of life menstruation took place, and the external genitalia were well developed and covered with hairs; uterus and ovaries had the size of those of a 20-year-old person. It is possible that this case belongs to primary hypergenitalism as well as a similar one of Pellizzi.[4]

Our positive knowledge of the etiology and pathologic anatomy is limited to those few cases. In a few observations premature sexual development has been ascribed to such early and excessive practices as masturbation and cohabitation due to seduction. Where such pathologic factors are absent, what the cause of the prematurity of the impulses for the somatic changes is remains a problem, as it is likewise not known why at a certain period of life under physiologic conditions certain organs should increase rapidly and perfect their function, the sexual glands particularly receiving impulses that cause a more rapid maturing. Though the nature of the primary stimuli that control these changes is not known, it is established that the endocrine glands in their interlocked and mutually affecting functions are of the greatest importance for the normal growth of the body and for sexual maturity, among them especially the genital glands, the adrenals, the pituitary body, the thyroid and the so-called "puberty-glands," the thymus and the pineal; their inextricable interaction in the main still defying analysis; the inner working of biologic laws, of the phylogenetic, hereditary and racial factors, of climate, etc., that regulate the onset of these processes remains obscure.

The following case of precocity was observed by me in the Cook County Hospital. The coincidence of imbecility renders the case more interesting and adds to the list of observations as exemplified by the reports of the authors before mentioned.

CASE REPORT

History.—K. W., 11½ years old, son of Ruthenian immigrants. The father is middlesized, of sturdy build, living at present out of Chicago; mother small. There were two other children with irrelevant histories. The patient was born at full term, weighed, allegedly, 7 pounds. He grew first slowly, more rapidly at 5 years of age; he has always been mentally much below par and somewhat hard of hearing, according to his mother's statement. He learns poorly, has a very poor memory and is in the first grade of the public school where he has attended for three years. He has had measles, scarlatina, diphtheria and whooping cough. He often snores and sleeps with open mouth. He began to grow rapidly about one year prior to this report; no information can be obtained from the mother about the sexual development of her boy; neither does she remember when he began to walk and talk.

Present Status.—The patient is of slender build, of blond type; height 1.51 m.; weight 85 pounds, with waist and coat off. The lower half of the body, measured from the lower edge of the symphysis to the heel, is 75 cm. The musculature is flabby and poorly developed; head rachitic, tubera frontalia and

Author's case of sexual precocity. Boy aged 11½ years.

parietalia prominent; fronto-occipital circumference, 55 cm.; there are twenty-eight perfect teeth; no trace of caries; chest poorly developed; chicken-breast deformity; circumference in nipple-line during middle respiratory position, 67.5 cm. The lower part of the abdomen is somewhat pendant, the muscles of the abdominal wall flabby and poorly developed. There is a slight degree of genu valga and beginning pedes valgi.

Genitalia.—In comparison with the age of the boy his genital organs are striking in their degree of development; there are also some secondary sexual characteristics present. The penis is 10.6 cm. long measured from the root at the symphysis to the end of the prepuce, and 9 cm. in circumference in the nonerected state. The prepuce reaches about 1 cm. beyond the glans. The testicles are of the size of those in the adult man, 3.5 cm. to 4 cm. long, the left larger than the right. There is an abundant growth of hair on the pubes, more than 5 cm. long; the upper border line is of feminine type; there is a conspicuous brown pigmentation of the median line from the mons veneris to the umbilicus. The scrotum is covered with a few hairs, 0.5 to 1 cm. long. In both axillae there are patches of skin of 1.5 to 2.5 cm. diameters that are covered with a crop of blond hair about 1 cm. long. The boy has vigorous erections of the penis, as was witnessed in the hospital. The prostate gland is of the size of that of an adult. Massage of the prostate and seminal vesicles, performed once, did not yield sperma. The larynx is very prominent, the voice strikingly deep.

The inner organs show no abnormal conditions; no tumor of the kidneys can be palpated, neither does roentgen-ray examination reveal any anomaly of these organs. The roentgenogram of the skull demonstrates a slightly enlarged sella turcica and a moderate increase in size of the skull. Roentgenograms of the hand show no deviation from the ossification that corresponds to the actual age of the boy. The ear drums are only slightly retracted, the hearing little affected.

Psychic Conditions and Habits.—The boy is very irritable; "nervous"; cries when his mouth is inspected. He is of a stubborn, disobedient, troublesome disposition, and resentful toward other children, and has to be reprimanded for it in the hospital. At home he prefers to play with boys younger than himself and shuns boys of his size; there are evidences of sexual shame; he chews his nails habitually; these are much bitten off. There seems to be at present no particular propensity to the other sex. He cannot count to more than five; even then he must be helped. He cannot write his name unless a copy is placed before him; his handwriting is hardly readable; nor can he do sums; he says for instance, 2 and 2 are 3, 2 and 2 are 6; 1 and 1 are 7. He is not able to say his prayers without being helped by his mother; he does not know any verses or any song, although he has attended, as mentioned before, the public school for three years. In fact, he is too dull to answer simple questions that refer to his own person, and during the examination he gives many evidences of a very poor memory even as to occurrences and experiences that would seem important to a normal boy.

Etiologically, the case may be classified as (primary) hypergenitalism without anatomicopathologic changes. The clinical examination excludes a tumor of the adrenals and there is no ground for suspecting a tumor of the pineal gland, corresponding cerebral symptoms being entirely wanting. Further, the makrogenitosomia praecox due to hypopinealism occurs only through premature destruction of functionating pineal tissue, that is, before the seventh year of life, since at that time the involution normally commences.

Against a hypophyseal affection (hyperpituitarism) militates the absence of such characteristic symptoms as were observed in the rare cases of acromegaly in adolescence and childhood. (Cases of Arnold, Claude, Schultze-Fischer, Hutinel, Pel and Salle, the two latter since birth. Quoted from Falta.[31]) The slight enlargement of the sella turcica hardly has any bearing in our case, considering the hydrocephalic increase in size of the skull of the boy.

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31. Falta, W.: The Ductless Glands (Translation from the German), p. 272.

PROGRESS IN PEDIATRICS

A REVIEW OF RECENT LITERATURE ON THE GENITO-URINARY DISEASES OF CHILDREN *

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VOLUME OF URINE

Addis and Watanabe[1] studied the daily volume of urine in adults on a standard diet and found that the volume of urine in any individual for any one day or part of a day is extremely variable in spite of constant water intake. They found that not less than 38 per cent. of the twenty-four hour volume was excreted during the first eight hours of the day, and not less than 53 per cent. in the first twelve hours. The night urine was never more than 47 per cent. of the total twenty-four-hour amount. Of course, the volume of urine excreted varies a good deal with the temperature, with the humidity, and with the number and character of the bowel movements, for if much fluid is excreted through these channels, there will be less excreted through the kidneys. Such studies are extremely valuable, as it is often necessary to know what the ratio between intake and output should be. As far as I know, no such work has been done with children, and it is rather difficult to decide sometimes in dealing with nephritic children, whether the urine output is as high as it should be in relation to the fluid intake.

CHEMISTRY OF URINE

C. U. Moore[2] discusses phenol excretion in the new-born and arrives at the following conclusions:

1. An increase in the number of stools per day is associated with a decrease in the total phenol output in the urine.

2. In a series of fifteen infants the phenol excretion per kilogram of body weight is less in the breast fed than in the artificially fed infant.

3. In infants and in adults, so far as it is possible to determine from the limited number of cases now at hand, there is an interrelation

* Submitted for publication Dec. 17, 1917.

1. Addis and Watanabe: Jour. Biochem., 1916, **27**, 267.
2. Moore, C. U.: Jour. Dis. Child., 1917, **13**, 15.

between the total phenol excretion and the protein intake as measured by the total nitrogen excreted in the urine. This relation can be expressed in the general term "trebling the protein intake doubles the phenol excretion."

4. Contrary to the earlier findings, phenol is quantitatively present in the urine of every new-born infant, the average of nineteen cases being 11.2 mg. for the first three days of life.

5. As phenol is present during the period of starvation, it must originate in part through endogenous metabolism.

Johnson and Veeder[3] have studied the nitrogen partition in the urine of normal children.

Urea nitrogen makes up from 80 to 85 per cent. and ammonia nitrogen from 3 to 5 per cent. The combined figure for the two is less than 90 rather than above 90 as in adults.

Creatin is constantly present, as is creatinin. The two combined form a smaller percentage than the creatinin alone in the adult. The amount of undetermined or "rest" nitrogen is high in children.

Torres[4] discusses the relation between the diet and the acidity of the urine, and proves that a suitable regulation of the diet is a most valuable adjunct to the various drugs which have been used for the purpose. He arrives at the following conclusions:

1. The difficulties which one often encounters in changing the reaction of the urine in children are very much diminished when a suitable diet is prescribd.

2. Diminishing the amount of protein in the diet to 2 gm. and sometimes to 3 gm. per kilogram will often in itself render the urine alkaline without using a drug.

3. In cases in which the amount of protein reaches the lowest physiologic limit without turning the urine alkaline, one may continue to diminish the acidity by adding vegetables to the diet.

4. In cases in which vegetables are used to turn the urine alkaline, one must use, if possible, vegetables in which the amount of protein is smaller in proportion to the salts, like fruits, rice, wheat, etc., rather than those which have a large amount of protein, as peas, beans, etc. Substances which contain purins, like coffee, tea and cocoa, may increase the acidity, because they may produce uric acid.

5. In cases of infection, especially in infections of the urinary tract, and in cases of starvation, the urine tends to become more acid than in other conditions; therefore, it is more difficult to render it alkaline.

3. Johnston, M. R., and Veeder, B. S.: Am. Jour. Dis. Child., 1917, **13,** 404.
4. Torres, C.: Am. Jour. Dis. Child., 1917, **14,** 365.

6. When drugs are used without the proper diet, the doses necessary to make the urine alkaline are much larger than is ordinarily believed.

7. The action of drugs (either acid or alkaline) is very fleeting; therefore, they should be given in large and frequent doses.

ANURIA

Clough[5] reports a case of prolonged anuria in a boy of 7. The boy had scarlet fever, and during the attack passed very little urine. When he came under the writer's care, soon after the attack, the anuria persisted, and for over a month he passed only from 2 to 6 ounces of urine a day. He never had any edema, nor any albumin, and on only one occasion were casts found in the urine. He made a good recovery.

CALCULUS

Lazelle[6] reports a kidney stone in a child of 7. The symptoms consisted of attacks of abdominal pain, acute in character, passing off usually in a few hours. The roentgen ray showed a stone in the kidney, and at operation two stones were successfully removed.

While ureteral and kidney stones are by no means so common in children as they are in adults, they are not so rare as has been generally believed, and a number of cases have been repeorted of late years, particularly by English writers.

TUMORS

O'Neil[7] says that bladder tumors in infants and children are distinctly rare. The great majority appear before the fifth year. They are of the connective tissue type, and are clinically and pathologically malignant, except in rare cases. Disturbances of micturition, shown by sudden retention or incontinence, are usually the earliest symptoms. Abdominal pain is a common symptom. The urine at first may show no abnormality; later signs of cystitis develop. As they do not tend to ulcerate at first, hematuria is often absent.

Early diagnosis and operation offer the only means of recovery.

Friedlander[8] reports a sarcoma of the kidney treated by roentgen ray. The tumor occurred in a boy of 4 and was so large that no surgeon was willing to attempt its removal. Roentgen-ray treatments were started and for a while the tumor grew smaller, but later increased in size. The child finally died of bronchopneumonia occurring during an attack of measles.

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5. Clough, F. E.: Am. Jour. Dis. Child., 1916, **11,** 367.
6. Lazelle: Northwest Med., 1916, **15,** 403.
7. O'Neill: Boston Med. and Surg. Jour., Dec. 9, 1915.
8. Friedlander: Tr. Am. Ped. Soc., 1916, **28,** 59.

The tumor examined at necropsy showed extensive degenerative lesions due to the roentgen ray, proving that the treatment was not without its effect on the tumor tissue.

ENURESIS

But little of importance has been written about enuresis recently. The very multiplicity of drugs and other measures that have been suggested to control this disorder show how little is really known about it.

Dunham[11] is an advocate of suggestion as a therapeutic measure in nocturnal enuresis. The condition, he believes, is not so common as is generally thought. Among 800 nervous children admitted to the Phipps Psychiatric Dispensary, ranging in age from 5 to 16 years, only 7 per cent. were bed wetters.

Many cases are due to pure nervousness and no abnormality of the urine or of the genito-urinary tract can be shown.

Dunham reports good results with his suggestive treatment, which he carries out as follows:

These four sentences are printed on a card.

1. I am not going to wet the bed.
2. I am going to wake up at midnight.
3. I shall get up and pass water.
4. I shall not wet the bed any more.

PYELITIS

R. M. Smith[12] discusses the mode of infection.

In favor of the ascending theory are the clinical data. Against it are the facts that colon bacilli have never been shown to pass up the normal unobstructed ureter, and that they have frequently been introduced into the bladder without causing any damage. He believes that the ascending theory has not been proved, and that the facts, experimental and otherwise, are against it.

The usual mode of infection is through the lymphatics, the colon bacilli invading the lymphatics from the intestinal tract, or from some focus elsewhere (particularly the vulva, in girls). From thence they pass into the blood, and from the blood to the kidney. After reaching the kidney they pass through the glomeruli and are excreted at the pelvis. They may be excreted without any damage, or may cause a pyelitis. Smith cites the case of a child who had a severe pyelitis secondary to a few impetiginous pustules on the neck. The cultures from the neck and from the urine showed *Staphylococcus aureus.*

11. Dunham, F. L.: Am. Jour. Dis. Child., 1916, **12,** 618.
12. Smith, R. M.: Am. Jour. Dis. Child., 1916, **12,** 103.

When the original focus of infection cleared, the pyelitis cleared up also. Smith explains the greater frequency of pyelitis in girls than in boys by the fact that the vulva, urethra and vagina are fine culture grounds for bacteria, which enter the lymphatics, blood, and finally the kidney, but that the infection does not ascend through the urethra.

Huet[13] likewise supports the theory of descending infection. He reports an epidemic of pyelitis which started in a child who had pyelitis secondary to a bronchitis. Four other children who were cared for by the same attendant later developed pyelitis. He believes it was transmitted by milk: that the attendant in changing the babies' diapers infected her hands and then the milk. The colon bacilli recovered from all the cases were of the same type, and Huet believes that this series of cases proves that occasionally, at any rate, infection may be per os.

Helmholz and Beeler[14] injected sixty-six rabbits with various strains of colon bacilli, and only two showed a typical pyelitis. Eleven rabbits were injected with a mixed culture of pneumococci and colon bacilli; of the eleven animals, six showed focal lesions of the kidney: three had pyelitis, one had cortical abscesses and two had diffuse hemorrhages into the cortex. Their conclusions follow:

1. It is possible to produce typical pyelocystitis in the rabbit by the intravenous injection of colon bacilli isolated from human cases.

2. If a mixture of organisms is injected, the relative number of kidney infections can be greatly increased.

Abt[15] brings up the point that sometimes in a case of pyelitis several specimens of urine have to be examined before any pus can be found. He tends to favor the ascending theory of infection, because it is so well supported by the clinical facts. *Fever* and *restlessness* are the two main symptoms. Forcing water is the most important single thing in the treatment. Abt recommends using very small doses of hexamethylenamin and believes the patient should be watched very carefully while taking it. He does not favor the vaccine treatment.

Levy and Strauss[16] find that the strength of formaldehyd necessary to inhibit the growth of the colon bacillus is a concentration of 1 to 5,000 or greater. Under a dose of 7 grains of hexamethylenamin three times a day (in adults) formaldehyd is never present in a concentration greater than 1 to 5,000. The only organism destroyed or inhibited by this concentration is the typhoid bacillus. For the destruction or inhibition of other organisms a high acidity of the urine is necessary, and this high acidity in combination with formaldehyd may produce injury of kidney tissue.

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13. Huet: Jahrb. f. Kinderh., December, 1915.
14. Helmholz, H. F., and Beeler, C.: Am. Jour. Dis. Child., 1917, **14**, 5.
15. Abt, I. A.: Med. Clinics of Chicago, 1916-1917, **2**, 895.
16. Levy and Strauss: Arch. Int. Med., 1914, **14**, 730.

Graves[17] discusses pyelitis with special reference to its occurrence in boys. He believes in the descending theory of infection. In the treatment of all cases of pyelitis in boys the intestine is to be recognized and dealt with as the potential source of the disease. The alkaline treatment is the best to follow in most cases. In all obstinate cases, autogenous vaccines should receive a trial.

Summary.—I believe at the present time it is fair to state that most authors favor the descending theory of infection. Opinions differ a good deal as to modes of treatment. Most agree that forcing fluid is of a good deal of value, and that vaccines may help somewhat in occasional chronic cases, but the relative virtues of the alkaline and of the acid-hexamethylenamin treatment have by no means been decided. A man of as great experience as Still recommends the alkaline treatment unreservedly, and barely mentions hexamethylenamin, and yet we know there are many cases of pyelitis which do not respond at all to alkalies. From what various men have written, it would seem that the alkali method of treatment will cure a good many cases, and that it is probably to be preferred to *small* doses of hexamethylenamin. Large doses of hexamethylenamin will, however, clear up many cases that have not responded well to small doses or to the alkali treatment. Such large doses are not entirely without danger, however, although by no means as dangerous as many writers state. The most reasonable method of treatment usually to follow, would, therefore, be to start with alkalies, and if good results are not apparent in two or three days, to use large doses of hexamethylenamin.

ORTHOSTATIC ALBUMINURIA

Jeanneret[18] thinks that "postural" albuminuria is the best name for the condition, as other factors besides orthostasis enter into its production. He studied the effect of lordosis and of various postures in causing albuminuria in 204 children. His results may be summarized as follows:

1. Many children with a fixed lordosis have no albuminuria.

2. In only 3 per cent. of the children studied could albuminuria be induced by causing the patient to be in an artificially lordotic position, and then only if the child was kept motionless.

3. Orthostasis alone caused albuminuria in only 1.3 per cent. of the children, and then only when the child was kept motionless. Therefore neither lordosis *alone,* nor the erect posture *alone* is enough to produce albuminuria.

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17. Graves: Am. Jour. Med. Sc., 1917, **154,** 548.
18. Jeanneret: Arch. de méd. d. enf., 1915, **18,** 46.

4. Lordosis and orthostasis combined, accompanied by movements of the legs, produced albuminuria in only 1.6 per cent.

5. The combination of the factors lordosis, orthostasis and immobility caused albuminuria in 49 per cent.

6. Sex, age and tuberculosis were found to have no etiologic significance.

Therefore, postural albuminuria is due not to a single factor, but to a combination of several.

When a child with a lordosis stands erect there is caused considerable venous stasis in the region of the kidney. Muscular contractions compensate for this by compressing the veins and helping the blood along with the aid of the valves, which are particularly numerous in the veins of the lower leg. If the muscular contractions are not vigorous enough, they do not suffice to compensate for the venous stasis that is caused by the lordosis and orthostasis, and albuminuria results.

These considerations are important in treatment. Nephritic albuminuria tends to disappear under the influence of rest; postural albuminuria tends to disappear under the influence of exercise, particularly of walking. This same exercise will exaggerate a nephritic albuminuria. Jeanneret believes, therefore, that children with postural albuminuria should be taken out of school for a few weeks, should be sent to the country, if possible, and made to exercise a great deal: in a word, exercise should be the specific remedy for postural albuminuria. The diet need not be restricted. The prognosis is excellent, and postural albuminuria never develops into nephritis. This is the most comprehensive study of the subject since that of Jehle, whose elaborate monograph appeared in 1909. Jehle believed that lordosis was the cause of albuminuria; Jeanneret seems to have proved that other factors are of equal importance.

Achard[19] calls especial attention to the fact that orthostatic albuminuria often first appears after infections which may have affected the kidneys. He believes that in orthostatic albuminuria the lordosis and the orthostasis are acting on an already damaged kidney. In the normal subject the erect attitude diminishes the ease with which the blood returns by the inferior vena cava and the renal veins. There results from this the passage of a certain amount of fluid from the vessels into the lower part of the body, and an increased concentration of albumin in the blood, which can be demonstrated by the refractometer. At the same time there is a transitory diminution of the arterial pressure, and of the volume of urine. Lordosis facilitates venous stasis and the transudation of albumin, but something else is necessary in order to

19. Achard: Rev. gén. de clinic et de thérap., 1916, **30**, 625.

bring about albuminuria, and this additional factor is a slightly damaged kidney. The therapeutic indications follow these etiologic lines. Achard recommends neglecting the damaged kidney and treating the lordosis. It is the weight of the head and of the trunk which causes lordosis, because they are insufficiently supported by feeble muscles. The following measures he believes of value in treatment:

1. Resting in a prone position two hours after dinner each day.
2. Avoiding attitudes that provoke lordosis.
3. Special exercises designed to strengthen the back muscles.
4. Massage and hydrotherapy for the general circulation.
5. Diet and general hygiene.

Janeway[20] discusses especially the diagnosis as follows:

> First put the patient to bed for a considerable period, to make sure that the urine becomes free from albumin after a reasonable length of time. The second specimen passed after going to bed ought to be albumin free, or we are not dealing with a case of postural albuminuria. After determining that the urine is free from albumin while the patient is flat on his back, we can have him stand in a markedly lordosed position against a wall for half an hour. This will usually produce extreme albuminuria, and on going to bed again the albumin will promptly disappear. Lordosis is an important, but not an essential factor; a considerable degree of lordosis may exist without albuminuria, and the albuminuria may exist without lordosis.

One interesting diagnostic point, according to Janeway, is that the majority of nephritics show only albumin coagulable by heat; orthostatic cases often show protein precipitated by acetic acid in the cold, which may be euglobulin.

The treatment consists in a correction of the posture, invigorating exercises and a full diet.

Barber and Smith[21] made phenolsulphonephthalein tests on six patients with orthostatic albuminuria. In four cases it was quite normal. In one case it was 5 per cent. lower than the usually accepted standard. In the other case it was 14 per cent. lower with the patient standing than it was when made in the recumbent position.

Hempelman[22] likewise investigated kidney function in orthostatic albuminuria by means of the phenolsulphonephthalein test. He found that the percentage of phenolsulphonephthalein excreted in two hours by normal individuals was not affected by position. In seven cases of orthostatic albuminuria the phenolsulphonephthalein test was from 58 to 86 per cent. When these patients were put in a lordotic position, producing a marked albuminuria, the total output of phenolsulphonephthalein in two hours was reduced on an average of 12.9 per cent.

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20. Janeway: Med. Clin. North America, 1917, **1,** 21.
21. Barker and Smith: Am. Jour. Med. Sc., 1916, **151,** 44.
22. Hempelman, T. C.: Am. Jour. Dis. Child., 1915, **10,** 418.

Beifeld[23] reports a case of orthostatic albuminuria cured by tonsillectomy and believes that chronically infected tonsils may occasionally be a contributing factor in causing the condition.

NEPHRITIS

The literature on nephritis in the adult in the last few years is enormous, but comparatively little has been written about the condition in children. Certain of the papers which have been written with especial reference to adults apply equally well to children, and for that reason a few of the more important ones are included here. Two things especially have interested investigators of nephritis in recent years, the functional capacity of the organ, and the classification of the different types of the disease. It is beginning to be realized that an accurate knowledge of the function of the kidney as a whole is more important to the clinician and to the patient than a knowledge of the particular type of damage that has been done to the various unit structures of the kidney as seen under the microscope, and for this reason pathologic studies have largely given way to chemical studies concerned with the power of the kidney to do its work.

The classification of nephritis has always been a most perplexing problem, and has never been very satisfactory. At present, authorities on the subject seem to be departing further and further from the old anatomic classifications, which recognized several types of both acute and chronic nephritis, and are tending to simplify the classification more and more, recognizing particularly clinical types of the disease rather than histologic types as shown under the microscope. This puts a complicated subject on a much simpler and clearer basis.

ETIOLOGY

Loeb[24] calls especial attention to tonsillitis as an important cause of nephritis.

1. Acute nephritis results from acute tonsillitis far more often than is usually believed.

2. The symptoms are not manifested until some time after the inception of the disease.

3. There are probably many cases in which a mild nephritis occurs incident to a tonsillitis, which goes on to resolution without the patient or physician being conscious of its presence.

4. It is incumbent on practitioners to examine the urine of every patient with tonsillitis, not only during the height of the disease, but for some time afterward as well.

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23. Beifeld: Jour. Lab. and Clin. Med., 1917, **2**, 638.
24. Loeb: Tr. Am. Laryngol., Rhinol. and Otol. Soc., 1910, p. 146.

5. Spontaneous, or "idiopathic" nephritis is probably often due to a tonsillitis that has not been considered as an etiologic possibiliy.

6. Chronic affections of the kidney may very well owe their origin to unrecognized acute attacks of nephritis of tonsillar origin.

7. Much light may be shed on this subject by a study of the urine in a large number of cases of acute tonsillitis.

Grulee and Gaarde[25] discuss involvement of the kidney as a result of focal infections, with especial reference to tonsillitis. They report six cases of acute hemorrhagic nephritis in children, following several days after an attack of acute tonsillitis. The urine is very bloody, almost as to suggest a hemorrhage into the bladder. There may also be a good many pus cells present, the pus cells tending to appear as the reds diminish in quantity. There are no uremic symptoms, no edema, and the condition is usually much improved or entirely cleared up in two or three weeks. Cultures from the throat agree in many cases with the urinary cultures (hemolytic streptococci or staphylococci). In some cases the removal of a focus of infection such as the tonsils is followed by an immediate clearing up of the urine.

Baxter[26] reports five cases of acute hemorrhagic nephritis secondary to infection of the post nasal space. Symptomatically, the children became well in about four weeks, but the ultimate clearing up of the urine took from two to four months in some cases.

Dick and Dick[27] made urine cultures from a number of cases of chronic nonsuppurative nephritis, with the following results:

> In all cases examined the urine contained numbers of bacteria, mostly anaerobes. In one case the bacterial flora of the urine was the same as that of a focus of infection in another part of the body. The bacteria isolated from the urine readily produced experimental nephritis. These facts lead us to believe that bacteria multiplying in the foci of infection frequently gain entrance to the blood stream and are excreted in viable condition through the kidneys, and that the excretion of bacteria in this way by the kidneys may be a common cause of nephritis.

The same authors[28] investigated a number of patients with evident focal infections to learn how frequently bacteria found in the focus of infection could be isolated from the urine, in what number they occurred in the urine, and whether excretion of bacteria might occur to any extent without clinical evidence of injury to the kidneys.

Eighteen patients were studied. In six of these the bacteria found in the urine did not correspond to those found in the focus of infection. In four cases a partial correspondence was found between the bacterial

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25. Grulee and Gaarde: Jour. Am. Med. Assn., 1915, **65,** 312.
26. Baxter: Arch. Pediat., 1916, **33,** 729.
27. Dick and Dick: Jour. Am. Med. Assn., 1915, **65,** 6.
28. Dick and Dick: Arch. Int. Med., 1917, **19,** 493.

flora of the urine and that of the focus of infection. In eight cases the correspondence was more striking.

Staphylococci and gram-positive anaerobic diphtheroids are common inhabitants of the urethra. In eight cases, aside from these organisms, one or more of the kinds of bacteria found in the urine were isolated from the focus of infection.

Such studies indicate the very great importance to the kidney of focal infections.

Frank[29] believes that most nephritides in childhood are secondary to acute infection of some sort elsewhere in the body. There are, however, types of nephritis in infancy that are apparently primary, and are not dependent on previous infection. In babies, gastro-intestinal disease is often a cause of nephritis. Frank calls especial attention to the fact that of twenty-two cases investigated by him pathologically, many were of the hemorrhagic type, which is a particularly common sort of nephritis in childhood.

CLASSIFICATION AND GENERAL CONSIDERATIONS IN NEPHRITIS

Langstein and Benfey[30] adhere closely to the earlier classification of Heubner. They recognize the following types of chronic nephritis in children:

1. Chronic hemorrhagic nephritis is particularly characteristic of children. It is characterized by occasional exacerbations of hematuria, and nearly always is accompanied by edema.

2. A second form is first shown by edema, but is accompanied by no blood in the urine. The urine contains a great deal of albumin and many casts. Infectious processes are likely to be the cause of the nephritis in the first group, and not so likely in the second.

3. Contracted kidney, or "interstitial" nephritis (very rare).

4. A parenchymatous nephritis secondary to pyelitis.

5. A form of nephritis coming on very insidiously and manifested by general debility of the child, called by Heubner "paedo nephritis levis." The urine contains a small amount of albumin, a few casts and leukocytes, and from time to time a few red blood cells. It is very likely to be a sequel of scarlet fever or tonsillitis.

6. "Intermittent" albuminuria. Rare and of little practical importance.

Christian[31] discusses the classification of chronic nephritis in adults. It is especially instructive to observe how he has done away with the old complicated anatomic classification. He says:

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29. Frank: Arch. f. Kinderh., 1914, **11,** 202.
30. Langstein and Benfey: Med. Klin., 1914, **23,** 5987.
31. Christian: Cleveland Med. Jour., 1917, **16,** 223.

As our knowledge stands today, it is wiser to drop the terms "interstitial," "parenchymatous," etc., very largely from our clinical classification, and to use instead simple descriptive terms which indicate with the chronic nephritis the presence or absence of hypertension or myocardial insufficiency. The old type of kidney classification has been based on a study of the end-result of the diseased process.

Porter[32] discusses the condition known as renal infantilism. This is a most interesting condition, which has been described by the English writers particularly. It is dependent on a contracted kidney with high blood pressure, of the same characteristics as so-called "interstitial" nephritis in the adult. Coexistent with the kidney condition is a state of infantilism. Porter's patient was 7 years old and weighed only 32½ pounds (should be about 49 pounds). There was incompleteness of calcification in all diaphyses, ossification was absent in the wrist bones, and the mental development corresponded to the stature of the child rather than to his age. He was very thirsty and passed a large quantity of urine of low gravity, containing a small amount of albumin and a few granular casts in the sediment. The bladder was of enormous capacity and he often voided 16 to 18 ounces at once.

The most striking symptoms in all the cases previously reported (looked up by Porter) were polydipsia, polyuria, enuresis and dry skin.

Parkinson[33] reports a case of nephritis without albuminuria. The child was 3½ years old, and had pneumonia, after which edema appeared. The urine showed no albumin, but microscopically showed a few red blood cells and casts.

He brings up the point that "latent" nephritis may be more common than is suspected.

It is doubtful whether such a condition should be called true nephritis. It corresponds rather to the condition spoken of as "acute renal irritation" which may occur in any acute fever. The pathologic text-books speak of it as "acute degenerative" nephritis.

H. Wessler[34] found that in nearly all of his nephritic cases in children, both acute and chronic, there was a distinct cardiac hypertrophy, often coming on as soon as two weeks after the onset of the nephritis. This was shown by percussion, by the fluoroscope and by roentgenograms.

Berkley and Lee[35] after a study of ninety-three cases of acute and chronic nephritis in children, have settled the question of blood pressure, which is one that had previously been in dispute. They found:

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32. Porter: Arch. Pediat., 1915, **32,** 85.
33. Parkinson: Brit. Jour. Child. Dis., 1916, **13,** 138.
34. Wessler: Arch. Int. Med., 1914, **14,** 516.
35. Berkley and Lee: Am. Jour. Dis. Child., 1917, **13** 354

1. The blood pressure is elevated in the nephritis of childhood, and occasionally to a marked degree. This applies to both acute and chronic nephritis.

2. Systolic and diastolic pressures are not increased to the same extent, the former averaging about 20 mm. Hg, and the latter about 10 mm. above normal.

3. The pulse pressure is increased, but the factor is not constant.

4. The blood pressure in chronic nephritis shows no constant elevation above that in acute nephritis.

5. The blood pressure may, in rare instances, be of prognostic value.

6. No relation has been found to exist between the blood pressure and the urinary findings.

7. Patients having marked edema showed a slightly higher average blood pressure than those with little or none. The difference is not great enough to warrant any definite conclusions.

8. Albuminuric retinitis is probably not common, even in cases showing a marked increase in blood pressure.

FUNCTIONAL TESTS

Kidney function in children has not been investigated so extensively as it has in adults.

Leopold and Bernhard,[36] in a series of children free from renal disease, found that the phenolsulphonephthalein excretion for two hours varied between 50 and 96 per cent., with an average of 70 per cent. Five cases of acute nephritis and five of chronic nephritis were studied. In both the acute and chronic cases the phenolsulphonephthalein excretion was diminished. The same authors found in normal children the following apportionment of the nonnitrogenous constituents of the blood. The total nonprotein nitrogen varied between 19 and 40 mg.; the urea nitrogen varied between 8 and 21 mg., the average being 12 mg.; the uric acid varied between 6 and 3.2 mg., the average being 1.8 mg. The creatinin varied between 0.5 and 4 mg., the average being 1.5 mg. The blood of sixteen children with renal conditions was examined. In acute nephritis the nonprotein nitrogenous constituents were found to be within normal limits, and in chronic nephritis they were usually increased.

Leopold and Bernhard arrive at the following conclusions:

1. Figures for the nonprotein nitrogenous constituents of the blood, as well as for the phenolsulphonephthalein excretion of children free from renal disease, are practically identical with the figures obtained from adults, and vary within the normal limits as the adult figures vary.

36. Leopold and Bernhard: Am. Jour. Dis. Child., 1916, **11**, 432.

2. The changes in these figures in children the subjects of renal disease corresponded with the changes observed in adults.

3. The importance of the tests for diagnosis and prognosis, amply demonstrated in adults, will in all probability hold true for children, although a more comprehensive series of cases is required definitely to establish this view.

Tileston and Comfort[37] found that the phenolsulphonephthalein excretion for normal children varied between 78 and 81 per cent., while the nonprotein nitrogen of the blood varied between 22 and 26 mg. per 100 c.c. of blood. They investigated three cases of acute nephritis, the phenolsulphonephthalein tests being 39 per cent., 56 per cent. and 54 per cent. The nonprotein nitrogen of the blood in these cases was, respectively, 64, 34 and 24 mg. per 100 c.c. blood. They arrive at the following conclusions:

1. The determination of the total nonprotein nitrogen and urea of the blood is of great assistance in the diagnosis of uremia, and as a guide to the treatment of nephritis, a marked increase in these substances indicating actual or impending uremia, and calling for a diet low in protein. In the diagnosis of nephritis it is inferior to other methods, because many cases of nephritis show no retention of nitrogen.

2. The phenolsulphonephthalein test is very valuable in the diagnosis of nephritis, showing probably better than any other one method the degree of impairment of renal function. In the diagnosis of uremia and as a guide to diet it is inferior to blood analysis, for a low phenolsulphonephthalein output may occur without retention of nitrogen.

3. These investigations of the blood and of the phenolsulphonephthalein excretion would appear to indicate a better secreting capacity of the child's kidney as compared with that of the adult.

Hill[38] investigated four different types of tests for kidney function in children.

Phenolsulphonephthalein Test.—In twenty-seven normal children the highest phenolsulphonephthalein test was 100 per cent., the lowest 64 per cent., thus giving an average of 76 per cent. The figures for children are therefore somewhat higher than those for adults. The test was performed on thirty-seven children with nephritis, of all degrees of severity. Twenty-one cases were acute, sixteen chronic. The average excretion of the twenty-one acute cases was 59 per cent., or 17 per cent. below the normal average. The average excretion of the sixteen chronic cases was 63 per cent., or 13 per cent. below the normal average.

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37. Tileston and Comfort: Am. Jour. Dis. Child., 1915, **10**, 278.
38. Hill: Am. Jour. Dis. Child., 1917, **14**, 267.

Added Salt and Urea Test.—This consisted in adding a weighed amount of sodium chlorid and urea to a standard diet, and then determining how much of the added substances could be excreted in twenty-four hours. This test was found to be of little practical value.

"Two-Hour" Renal Test.—The "two-hour" renal test of Hedinger and Schlayer was performed in sixteen cases of nephritis and was found to be of considerable value in determining the degree of damage to the kidney. The principle of this test is that a normal kidney can vary the concentration of the urine from hour to hour; a nephritic kidney is likely to lose this ability. This is an extremely delicate test, and very easy to perform; hence it is of considerable practical value.

Blood Urea Nitrogen.—The concentration of blood urea nitrogen was determined in twelve nephritic children and was found to be slightly increased in some, normal in others. In general, the more severe the case appeared clinically, the more retention of urea was there likely to be. This is not a very valuable test for use in children.

The most valuable of the four tests are the phenolsulphonephthalein and the two-hour renal test, and they are valuable not especially in *diagnosis,* but more particularly in *prognosis.*

Zondek[39] believes that in considering kidney function it is not correct to look on salt and nitrogen as two separate factors without influence on each other.

Many times we see a kidney which may retain salt and put out nitrogen well, but when we cut down the nitrogen intake the salt excretion improves remarkably. Also, by adding a large amount of nitrogen to the diet, we can diminish the kidney's power of putting out salt. Occasionally we can even make a normal kidney hold back nitrogen by adding an excessive amount of salt to the diet. A salt-free diet is beneficial in reducing blood nitrogen. The question of fluid intake comes in as a third factor, to which a similar rule to the two other factors (sodium chlorid and nitrogen) is attributed. This rule seems to make an exception in the case of Schlayer's vascular hyposthenuria during the stage of regeneration of an acute nephritis, where, on account of the decreased power of the kidney to concentrate solids, there is copious diuresis due to the large amount of salt that is being excreted (getting rid of edema), for there is also increased nitrogen output with this increased salt excretion.

The salt concentration of the urine is greater during the daytime, the nitrogen concentration during the night. Normally, Bowman's capsule cares for salt, water and nitrogen excretion. This does not hold, however, for an injured kidney. Damaged kidneys function in an entirely different manner from healthy ones. It is not at all pos-

39. Zondek: Ztschr. f. klin. Med., 1915, **82**, 78.

sible to say that any given part of a diseased kidney excretes any given substance or substances. In a damaged kidney, if the damage is particularly to the glomerulus, let us say, the work of excreting salt and nitrogen falls on the tubules, and they might perhaps be able to excrete a fair amount of salt or of nitrogen *alone,* but not of both together. If in feeding a patient with nephritis, little or no salt is given, the tubules can concern themselves with nitrogen excretion alone and do it efficiently.

Zondek has found a diminution in the concentration of nonprotein nitrogen of the blood even when a nephritic child was taking as much as 120 gm. of protein daily, if the diet was salt-free. This is a rather new conception of kidney function, and Zondek in closing his paper makes a special plea for more individualization and less of routine in prescribing the diets of nephritic children.

TREATMENT

Hutinel,[40] in 1910, summed up in a few words most succinctly the principles to follow in treating nephritis in children. He said:

> Let me insist that in dealing with these nephritic children it is especially important to pay attention to careful nursing and hygiene. It is by these measures that the malady is cured, or in the more serious forms, that life is prolonged. Use drugs as little as possible. Especially is it important not to irritate the kidney and to forbid the patient eating any substances whose end-products he cannot eliminate. It is necessary, moreover, to do away with any coexisting infection, however insignificant it may appear, and to watch carefully the mouth, digestive tract, respiratory apparatus, skin, etc. In a word, one must remember that the kidney is delicate, and spare it as far as possible.

This was written seven years ago, but it holds equally well for the principles of treatment today.

Janeway[41] believes that often in dealing with chronic nephritis the protein intake is cut down unnecessarily. He says:

> To tell every patient with albuminuria or hypertension to stop eating red meat, or still worse, as I have actually seen done, to go on a milk diet, is evidence either of colossal ignorance or of inexcusable mental laziness. If the phenolsulphonephthalein test is normal I see no reason for restriction of the protein, either qualitatively or quantitatively, below a moderate normal intake.

Epstein[42] discusses the type of nephritis ordinarily called "chronic parenchymatous," with especial reference to treatment. This is the type of nephritis which is usually associated with the "large white kidney" spoken of in the textbooks, and one of the most striking clinical manifestations of it is the development of edema, which may often

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40. Hutinel: Bull. méd., Paris, 1910, **24,** 95.
41. Janeway: Am. Jour. Med. Sc., 1916, **151,** 158.
42. Epstein: Am. Jour. Med. Sc., 1917, **154,** 638.

reach an extreme degree. It is in this condition that the salt-free diet first advocated by Widal and his co-workers has been so successful, and the most generally accepted view of the causation of the edema is that the kidney is unable to excrete salt, and that the water retention is secondary to this. Epstein believes that other factors are perhaps of more importance than salt retention. He has proved that there is a considerable diminution of the protein of the blood serum which is caused by the continuous albuminuria, and that sometimes a nephritic of this type may lose over 20 gm. of protein a day in the urine. As a result of the decrease of protein in the blood serum there is caused a decrease in the osmotic pressure of the blood, which favors the absorption of fluid by the tissues. Therefore, in this particular type of kidney disease, a high and not a low protein diet is indicated. A diet containing a large quantity of protein with a minimum of carbohydrate and fat is the most efficient. The carbohydrate is restricted to promote a maximum assimilation of protein, and to exclude the greater production and retention of water which is incidental in the metabolism of carbohydrates. The fats are excluded because of the marked increase of fatty substances in the blood. The fluid allowed is restricted to the quantity present in the food, plus that which is necessary for the comfort of the individual patient. Enough salt is allowed to make the food palatable.

The diet is made up largely of the following articles: Lean veal, lean ham, whites of eggs, oysters, gelatin, lima beans, lentils, split peas, green peas, mushroom, rice, oatmeal, bananas, skimmed milk, coffee, tea and cocoa.

Christian[43] has studied extensively the use of diuretics in nephritis. In most patients with acute nephritis the kidneys will not respond to diuretics and diuretics are likely to do more harm than good. In chronic cases in which edema is of renal origin, diuretic drugs have very little effect in increasing urine output; in the group in which most of the edema is due to cardiac insufficiency, diuretics may work wonders. Theophyllin (theocin) is the best diuretic, but is likely to produce nausea. In nephritis, reduction of fluid intake salt poor diet, sweating and purging are the best methods of removing edema.

Harris[44] reports several cases of nephritis treated with epinephrin. Ten minims of a 1 to 1,000 solution injected subcutaneously once a day were found to diminish albuminuria and edema. Often a marked diuresis was caused by it.

Ercolani[45] likewise discusses the use of epinephrin in nephritis. He believes that the adrenals suffer injury in nephritis as well as the

43. Christian: Dominion med. Monthly, 1917, **49,** 25.
44. Harris: Liverpool Med. and Chir. Jour., 1916, **36,** 85.
45. Ercolani: Gazz. d. Osp., 1917, **38,** 321.

kidney itself, and that disturbances of the myocardium or of the nervous system in nephritis may be due to a lack of adrenal secretion. According to Ercolani, epinephrin is detoxicating and vasoconstricting in nephritis, both of which processes counteract the infection and ward off injury from the kidneys.

Morse[46] discusses the Edebohls operation as a therapeutic measure in the nephritis of children and carefully analyzes twenty-three cases in which it was performed. He concludes:

> Edebohls' operation is of much value in properly selected cases of nephritis in childhood. It may save life and result in permanent cure in acute nephritis. No child ill with acute nephritis should be allowed to die, therefore, without giving it the advantage of the chance afforded by this operation. It may prolong life for considerable periods in a not inconsiderable number of cases of chronic nephritis, and may possibly, in rare instances, result in cure. It should, therefore, always be considered in all cases of chronic nephritis in childhood which are not responding reasonably well under medical treatment.

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46. Morse: Jour. Am. Med. Assn., 1917, **69**, 525.

CURRENT PEDIATRIC LITERATURE

ANATOMY AND PHYSIOLOGY

Birth Weight, Average, in 2,000 Confinements.—S. P. Warren.
Am. Jour. Obst. and Dis. Women and Child., 1917, **76,** 932.

Growth, Children's, Anthropometric Photographic Control of.—L. Jeanneret and G. Messerli.
Rev. méd. de la Suisse romande, 1917, **37,** 570.

Ossification Processes in Supernumerary Fingers.—L. D. Chambardel.
Bull. de l'Acad. de méd., Paris, 1917, **78,** 656.

Patella, Physiologic Segmentation of.—P. Reinbold.
Rev. méd. de la Suisse romande, 1917, **37,** 653.

Temperature, Drugs that Influence.—R. Isenschmid.
Cor.-Bl. f. schweiz. Aerzte, 1917, **47,** 1610.

HYGIENE

Consulting Stations for Healthy Infants.—G. B. Allaria.
Riv. clin. pediat., 1917, **15,** 561.

BACTERIOLOGY AND PATHOLOGY

Achondroplasia, Case of.—S. de Stefano.
Pediatria, Naples, 1917, **25,** 655.

Angioneurotic Edema, Five Generations of.—J. R. and T. R. Crowder.
Arch. Int. Med., 1917, **20,** 840.

Biliary Cirrhosis, Infantile.—S. Ganguli.
Indian Med. Gaz., 1917, **52,** 361.

Carcinoma, Primary of Liver, in Infancy and Childhood.—J. P. C. Griffith.
Am. Jour. Med. Sc., 1918, **155,** 79.

Goiter, Return of, after Operation.—A. Sarkissiantz.
Rev. méd. de la Suisse romande, 1917, **37,** 525.

Goiter, Symposium on.—T. Kocher, et al.
Cor.-Bl. f. schweiz. Aerzte, 1917, **47,** 1633, et seq.

Jaundice, Chronic Hemolytic.—K. Faber and E. Meulengracht.
Hospitalstid., 1917, **60,** 1069

Jaundice, Focus of Infectious.—J. Kamp and T. B. Wernoe.
Ugeskr. f. Laeger, 1917, **79,** 1777.

Myasthenia Gravis; Report of Three Cases.—L. M. Crafts.
Journal-Lancet, 1917, **37,** 774.

Osteomyeloma, Multiple, with Albumosuria.—A. Testi.
Riforma med., 1917, **33,** 1073.

Thorax, Pathogenesis of Congenital Depression in.—R. Simonini.
Riv. clin. pediat., 1917, **15,** 595.

METABOLISM AND NUTRITION

Acidosis and Internist.—J. S. Lankford.
Texas State Jour. Med., 1917, **13,** 272.

Acidosis, Studies of, Determination of Betaoxybutyric Acid, Aceto-Acetic Acid and Acetone in Urine.—D. D. Van Slyke.
Jour. Biol. Chem., 1917, **22,** 455.

Acidosis, Studies on. Immediate Cause of Death in Acidosis of Nephritis.—J. L. Whitney.
Arch Int. Med., 1917, **20,** 931.

Acidosis, Varying Susceptibility of Children to.—M. Sawyer, F. A. Stevens and L. Baumann.
Am. Jour. Dis. Child., 1918, **15,** 1.

Beriberi, Infantile, Sugar Content of Blood in.—T. Suzuki.
Sei-I-Kwai Med. Jour., 1917, **36,** 109.

Deficiency Diseases.—D. J. H. Pol.
Nederl. Tijdschr. v. Geneesk., 1917, **2,** 1212.

Feeding of Infants with Congenital Debility.—A. Mola.
Le Nourrisson, Paris, 1917, **5,** 329.

Milk in Infant Feeding.—A. B. Marfan.
Le Nourrisson, Paris, 1917, **5,** 360.

Nursing, Maternal, Conservation of.—G. E. Baxter.
Illinois Med. Jour., 1917, **132,** 381.

Phosphate, Dicalcium, Availability of, when Present as a Constituent of Infant's Food.—H. I. Bowditch and A. W. Bosworth.
Boston Med. and Surg. Jour., 1917, **177,** 864.

Rachitis Developing at Thirteen.—B. Ricklin.
Cor.-Bl. f. schweiz. Aerzte, 1917, **47,** 1586.

Rickets, with Especial Reference to Premature Infants.—E. J. Huenekens.
Journal-Lancet, 1917, **37,** 804.

Spasmophilia and Milk.—K. O. Larsson.
Svens. Läk.-Sällsk. handl., Stockholm, 1917, **43,** 775.

ACUTE INFECTIOUS DISEASES

Acute Infections, Foreign Protein Injections in Treatment of.—J. G. Cross.
Journal-Lancet, 1917, **37,** 764.

Communicable Diseases, Relation of, to Community and to Physician.—M. F. Boyd.
Iowa State Med. Soc. Jour., 1917, **7,** 457.

Contagious Diseases, Hospital Care of.—L. A. Butler and V. Rau.
United States Naval Med. Bull., 1918, **12,** 27.

Diphtheria Carriers, Six Cases of Tonsillectomy in.—C. C. Ballantyne and B. S. Cornell.
British Med. Jour., 1917, **2,** 686.

Diphtheria Bacilli, Differentiation of.—S. Costa, J. Troisier and J. Dauvergne.
Bull. et mém. Soc. méd. d. hôp., 1917, **41,** 991.

Diphtheroid Bacilli, Diphtheria and.—C. Kling and M. Ljungdahl.
Svens. Läk.-Sällsk. handl., 1917, **43,** 721.

Diseases from Filtrable or Ultramicroscopic Germs, Clinical Picture of.—U. Gabbi.
Riforma med., 1917, **33,** 1013.

Measles, Cases of Laryngeal Stenosis as a Complication of.—M. F. Morris, Jr.
New York Med. Jour., 1917, **106,** 1125.

Measles, Sudden Ataxia with Ophthalmoplegia in Child After Recovery.—G. Morelli.
Policlinico, Rome, 1917, **24,** 1311.

Meningitis, Case of Fulminant Spinal Cerebrospinal Fever without.—W. St. C. Symmers.
Brit. Med. Jour., 1917, **2,** 789.

Meningitis, Cerebrospinal, Serum Sickness in.—C. B. Ker.
Lancet, London, 1917, **2,** 822.

Meningitis, Cerebrospinal, a Case of, Due to Streptococcus—M. Takeda and M. Maruta.
Bull. Naval Med. Assn., Tokio, 1917, No. 16, p. 2.

Meningitis, Different Forms and their Diagnosis.—E. E. Graham.
Pennsylvania Med. Jour., 1917, **21,** 158.

Meningitis, Pneumococcus.—G. Panayotabin..
Bull. et mém. Soc. méd. d. hôp., 1917, **41,** 1015.

Meningitis, Precipitation of Cerebrospinal Fluid in Diagnosis of.—S. Tashiro and A. Levinson.
Jour. Infect. Dis., 1917, **21,** 571.

Meningococcus Meningitis in New-Born.—D. J. M. Miller.
Arch. Pediat., 1917, **43,** 824.

Meningococcus, Recent Serologic Work on.—F. W. Andrewes.
Lancet, London, 1917, **2,** 847.

Paralysis, Infantile, Electrical Treatment of.—E. H. Grubbe.
Illinois Med. Jour., 1917, **132,** 384.

Paralysis, Infantile, Treatment of.—F. G. Hodgson.
Georgia Med. Assn. Jour., 1917, **7,** 168.

Pneumonia, Lobar, in Children.—G. Werley.
Southwestern Med., 1917, **1,** 18.

Pneumonia, Optochin in.—J. de Hartogh.
Nederl. Tijdschr. v. Geneesk., 1917, **2,** 1229.

Poliomyelitis, Acute.—A. S. Bosworth.
West Virginia Med. Jour., 1917, **12,** 208.

Poliomyelitis, Communicability of.—H. L. Amoss.
West Virginia Med. Jour., 1917, **12,** 209.

Poliomyelitis, Epidemic (1916); Description of Characteristic Sign.—H. Heiman.
Arch. Pediat., 1917, **34,** 846.

Poliomyelitis, Epidemic in Marion County, W. Va., July 26 to Oct. 7, 1917.—P. Noe, Jr.
West Virginia Med. Jour., 1917, **12,** 214.

Poliomyelitis, Microscopic Demonstration of Cocci in Central Nervous System in Epidemic.—L. Hektoen, G. Mathers and L. Jackson.
Jour. Infect. Dis., 1917, **22,** 89.

Poliomyelitis, Recent Additions to Knowledge of.—E. A. Rich.
Northwest Med., 1917, **16,** 372.

Rabies, Present Status of Treatment of.—C. R. Mejia.
Semana méd., 1917, **24,** 381.

Typhus at Madrid in 1916.—G. Marañon.
Siglo méd., 1917, **64,** 808.

Whooping Cough in Young Infants.—G. Railliet.
Le Nourrisson, Paris, 1917, **5,** 344.

TUBERCULOSIS AND SYPHILIS

Pott's Disease, Treatment of by Autogenous Tibial Bone Grafts.—T. Ambrose.
Med. Jour. of Australia, 1917, **2,** 413.

Syphilis, Alleged Dental Stigmata of.—V. Galippe.
Bull. de l'Acad. de méd., 1917, **78,** 501.

Tubercle Structure in Dermatologic Diagnosis.—W. L. L. Carol.
Nederl. Tijdschr. v. Geneesk., 1917, **2,** 1201.

Tuberculosis in Children.—G. H. Cattermole.
Northwest Med., 1917, **15,** 362.

Tuberculosis in Serbian Refugees.—Petrovich.
Bull. de l'Acad. de méd., Paris, 1917, **78,** 649.

GASTRO-INTESTINAL SYSTEM

Cyclic Vomiting in Relation to Acid Intoxication.—J. Loudon.
Canadian Med. Assn. Jour., 1917, **7,** 1084.

Diarrhea, Infantile, Chlorin Water in Treatment of.—S. Rosebery.
Brit. Med. Jour., 1917, **2,** 789.

Digestive Disease in Infants, Classification of.—A. B. Marfan.
Le Nourrisson, Paris, 1917, **5,** 321.

Enteric Infection Accompanied by Greenish Stools, Way to Cure Child of.—L. F. Robinson.
South Carolina Med. Assn. Jour., 1917, **13,** 768.

Enteritis in Infants, Fluid Extract of Salicaria in Treatment of.—H. DuFour.
Bull. Soc. méd. d. hôp., 1917, **41,** 1029.

Hernia in Children.—J. Brossy.
Rev. méd. de la Suisse romande, 1917, **73,** 525.

Intradermal Reactions to Proteins of Infants Suffering from Gastro-Enteric Disorders.—V. D. Greer.
Arch. Pediat., 1917, **34,** 810.

Indigestion, Protein, in Infant.—J. Zahorsky.
Missouri State Med. Assn. Jour., 1917, **14,** 520.

Megacolon, a Case of.—T. B. Noble.
Am. Jour. Obst. and Dis. Women and Child., 1917, **76,** 946.

Pyloric Stenosis in Infancy; Three Cases.—B. K. Rachford.
Arch. Pediat., 1917, **34,** 803.

BLOOD AND CIRCULATORY SYSTEM

Chlorin in Blood of New-Born.—S. Cannata.
Pediatria, Naples, 1917, **25,** 641.

Heart Defects, Congenital: Two Cases.—G. Bergmark.
Svens. Läk.-Sällsk. handl., 1917, **43,** 553.

Tachycardia, Paroxysmal, Cases of, in Children.—H. Koplik.
Am. Jour. Med. Sc., 1917, **154,** 834.

NERVOUS SYSTEM

Amaurotic Family Idiocy (Tay-Sachs' Disease), Two Cases of.—C. W. Rand.
California State Jour. Med., 1917, **15,** 503.

Amaurotic Family Idiocy or Infantile Degeneration, with Symmetrical Bilateral Blindness.—E. J. Bernstein.
Med. Rec., New York, 1917, **92,** 1074.

Cretinism, Sporadic, Three Cases of, in One Family.—C. Herrman.
Arch. Pediat., 1917, **34,** 831.

Epileptic Make-up, Diagnostic Importance of Recognizing Absence of, in States Simulating Idiopathic Epilepsy.—L. P. Clark.
Boston Med. and Surg. Jour., 1917, **177,** 915.

Habit-Spasm, So-called and St. Vitus' Dance.—C. W. Burr.
Pennsylvania Med. Jour., 1917, **21,** 163.

Hydrocephalus, Internal, Some Aspects of.—C. G. Leo-Wolf.
New York State Jour. Med., 1917, **17,** 555.

Mentally Impaired Children, Treatment of Hypoplastic and.—E. B. McCready.
Med. Rec., New York, 1917, **92,** 1015.

Neuroses, Minor, of Childhood.—J. Epstein.
Am. Jour. Obst. and Dis. Women and Child.—1917, **76,** 1027.

GENITO-URINARY SYSTEM

Kidney, Mixed Cell Tumor of, Weighing Three Pounds in Infant Ten Months Old.—W. E. Darnall.
Am. Jour. Obst., 1917, **76,** 786.

Nephrotomy for Complete Suppression of Urine in Child.—H. I. Holmes.
Med. Jour. Australia, 1917, **2,** 333.

Pseudohermaphroditism, Case of.—H. D. Purdum.
Am. Jour. Obst., 1917, **76,** 813.

Pyelocystitis in Infancy and Childhood.—H. F. Helmholz.
Illinois Med. Jour., 1917, **32,** 311.

OSSEOUS SYSTEM

Bone Disease, Roentgen Diagnosis of.—P. M. Lund.
Repert. de med. y cirug., Bogata, 1917, **9,** 44.

Osteoarthritis of Hip Joint, Study of Operative Treatment of.—M. Ozarki.
Boston Med. and Surg. Jour., 1917, **177,** 679.

Osteogenesis Imperfecta (Osteopathyrosis, Fragilitas Ossium); Report of Two Cases.—H. R. Mixsell.
Arch. Pediat., 1917, **34,** 756.

SKIN AND APPENDAGES

Eczema, Treatment of, in Childhood.—C. J. White.
Boston Med. and Surg. Jour., 1918, **178,** 5.

Ringworm and Allied Skin Diseases in Australia.—H. Priestley.
Med. Jour. of Australia, 1917, **2,** 471.

Ringworm Epidemic Presenting New Type of Fungus.—C. N. Paul.
Med. Jour. of Australia, 1917, **2,** 496.

Skin Diseases, Allergy with.—W. Lutz.
Cor.-Bl. f. schweiz. Aerzte, 1917, **47,** 1601.

Urticarias, Classification of.—R. L. Sutton.
Jour. Cutan. Dis., 1917, **35,** 749.

Xeroderma Pigmentosum, Carbon Dioxid Snow in Treatment of.—S. Lomholt.
Hospitalstid., 1917, **60,** 933.

EYE, EAR, NOSE AND THROAT

Cough, Reflex, from Foreign Body in Ear.—J. de la Cruz Correa.
Semana méd., 1917, **24,** 384.

Crystalline Lens, Embryonal Growth Center in.—A. Vogt.
Corr.-Bl. f. Schweiz. Aerzte, 1917, **47,** 1342.

Deafness, Complete Unilateral, Resulting from Acute Parotitis; Report of Case.—G. H. Willcutt.
Laryngoscope, 1917, **27,** 811.

Eye Disease, State Examinations and Treatment for, in Schoolchildren.—A. Rovinsky.
New York Med. Jour., 1917, **106,** 978.

Eyes, Care of, of Schoolchildren.—S. H. Monson.
Ohio State Med. Jour., 1917, **13,** 813.

Eyeground Examinations in Infants after Delivery with or without Instruments, Importance of.—J. A. Kearney.
Am. Jour. Obst. and Dis. Women and Child., 1917, **76,** 904.

Nasal Septum Deformity in Children. Study of 314 Children.—L. G. Kaempfer.
Laryngoscope, 1917, **27,** 868.

Otitis, Colon Bacillus.—R. Lund.
Ugesk. f. Læger, 1917, **79,** 1565.

Otitis Media, Acute, in Childhood.—G. B. Wood.
Pennsylvania Med. Jour., 1917, **21,** 156.

Tonsil and Adenoid Operations, Probable Cases of Fatalities at.—J. D. Mortimer.
Practitioner, London, 1917, **99,** 482.

Tonsil Operation, Use of Hemostat in.—J. Prenn.
Boston Med. and Surg. Jour., 1917, **177,** 917.

Tonsils, Accessory, Case of.—J. A. Hagemann.
Laryngoscope, 1917, **27,** 906.

Tonsils, Diseased; Influence on Health and Technic of Removal.—L. H. Lanier.
Arkansas Med. Soc. Jour., 1917, **14,** 147.

Tonsils, Removal of, as Prophylactic Measure in All Children of Four Years of Age, Why and How.—R. W. Perry.
Northwest Med., 1917, **16,** 339.

Xerophthalmia, Carbohydrate Dyspepsia and.—H. Rønne.
Ugesk. f. Læger, 1917, **79,** 1488.

Tonsillectomy, Painless and Bloodless.—W. W. Fowler.
Texas State Jour. Med., **13,** 286.

SURGERY AND ORTHOPEDICS

Ankylosis, Treatment of, by Interposition of Tissue.—E. M. Olivieri.
Semana méd., 1917, **24,** 153.

Cleft Palates, Davies-Colley Flap Opeeration in.—A. V. Smelker.
Southwestern Med., 1917, **1,** 34.

Cleft Palate, Occurrence of.—J. E. Frazer.
Practitioner, London, 1917, **99,** 401.

Jaws, Correction of Deformed.—P. Robin.
Bull. de l'Acad. de méd., Paris, 1917, **78,** 653.

Hip Joints, Much Altered, Good Functining in.—P. Haglund.
Svens. Läk.-Sällsk. handl., 1917, **43,** 611.

Tibia, Subperiosteal Fissure Fractures of, in Children; Report of Cases.—S. Kleinberg.
Am. Jour. Orthop. Surg., 1917, **15,** 764.

THERAPEUTICS

Blood Serum, Therapeutic Use of.—R. G. Freeman.
Arch. Pediat., 1917, **34,** 773.

Esophagoscopy and Tracheobronchoscopy.—A. Forero.
Repert. de med. y cirug., Bogatá, 1917, **9,** 2.

Heliotherapy and Pigmentation.—L. Jeanneret and F. Merserli.
Rev. méd. de la Suisse romande, 1917, **37,** 668.

Incontinence of Urine, Pituitary Extract in Treatment of.—N. A. Miklailoff.
Russk. Vrach, 1917, **16,** 417.

Leishmaniosis, Internal, Introduction of Antimony Into, Treatment of.—R. Jemma.
Riforma med., 1917, **33,** 1007.

Saline Solution, Intraperitoneal Injection of.—K. D. Blackfan and K. F. Maxcy.
Am. Jour. Dis. Child., 1918, **15,** 19.

Vaccine Therapy for Children.—P. Ceppellni.
Pediatria, Naples, 1917, **25,** 661.

MISCELLANEOUS

Abnormalities, Congenital, Two Cases of Unusual.—D. M. Greig.
Edinburgh Med. Jour., 1917, **19,** 383.

Birth Rate in Registration Area of United States.—F. L. Adair.
Journal-Lancet, 1917, **37,** 796.

Birth Rate, Menace of.—R. J. A. Berry.
Med. Jour. of Australia, 1917, **2,** 491.

Blue Disease, Case of.—E. Odriozola.
Cronica med., 1917, **34,** 320.

Cellulitis, Fatal Case of Pelvic, in a Child.—F. C. Pybus.
Brit. Jour. Child. Dis., 1917, **14,** 192.

Child, Protection of, Among Ancient Romans. IV.—E. Jeanselme.
Presse méd., 1917, **25.**

Dental Service for Schoolchildren, Petersham Plan for.—W. R. Woodbury.
Boston Med. and Surg. Jour., 1917, **177,** 834.

Delinquents, Juvenile, Survey of.—H. K. Faber and A. J. Ritter.
Am. Jour. Dis. Child., 1917, **14,** 444.

Emotional Life of Child.—C. P. Oberndorf.
Arch. Pediat., 1917, **34,** 747.

Feeblemindedness and Delinquency.—J. E. W. Wallin.
Mental Hyg., 1917, **1,** 585.

Health Examination of Bengali School Boys.—R. C. Ray.
Indian Med. Gaz., 1917, **52,** 386.

Lypodystrophia Progressiva, Case of, in Male.—F. P. Weber.
Brit. Jour. Child. Dis., 1917, **14,** 179.

Maternity and Child Welfare in Dublin County Borough.—E. G. A. Webb.
Dublin Jour. Med. Sc., 1917, **144,** 86.

Speech Correction—New Medical Study and Educational Movement.—W. B. Swift.
Boston Med. and Surg. Jour., 1917, **177,** 811.

Pyrexia, Significance of, in Infants.—W. W. Harper.
Med. Rec., New York, 1917, **92,** 805.